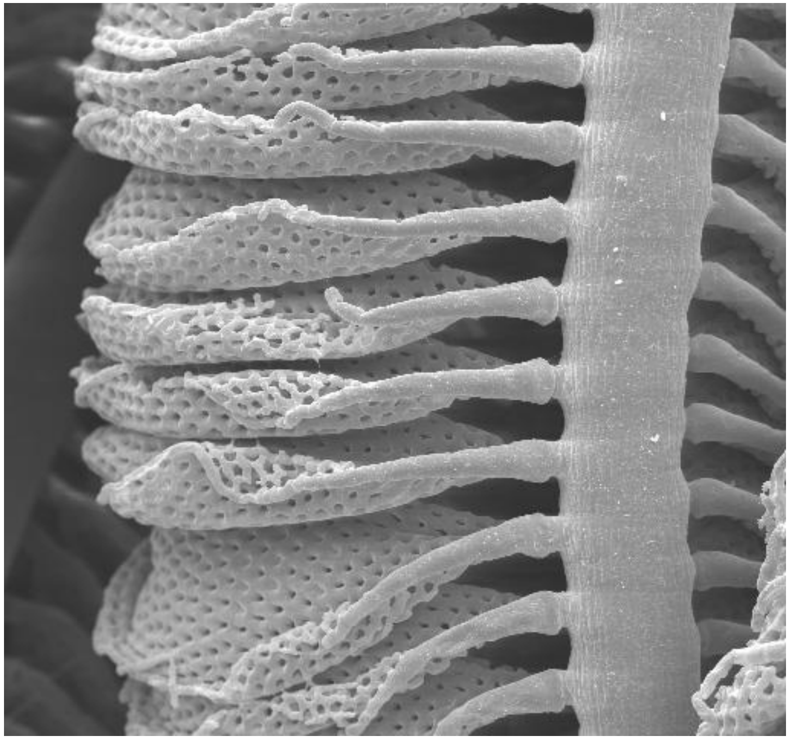
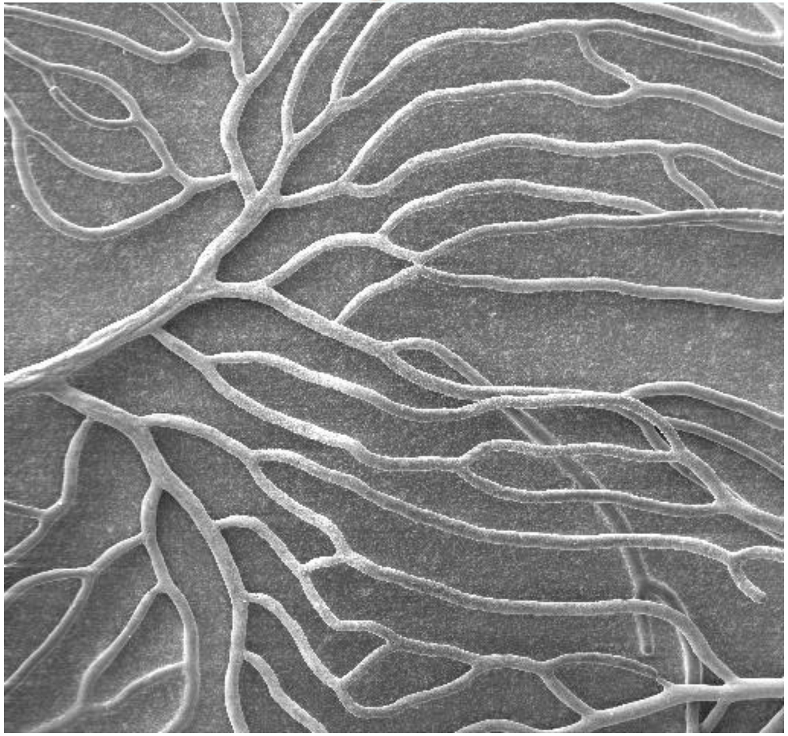
Principles of animal morphogenesis

Intro

Francois Fagotto, Prof. UM + team at CRBM-CRNS
Email: francois.fagotto@crbm.cnrs.fr



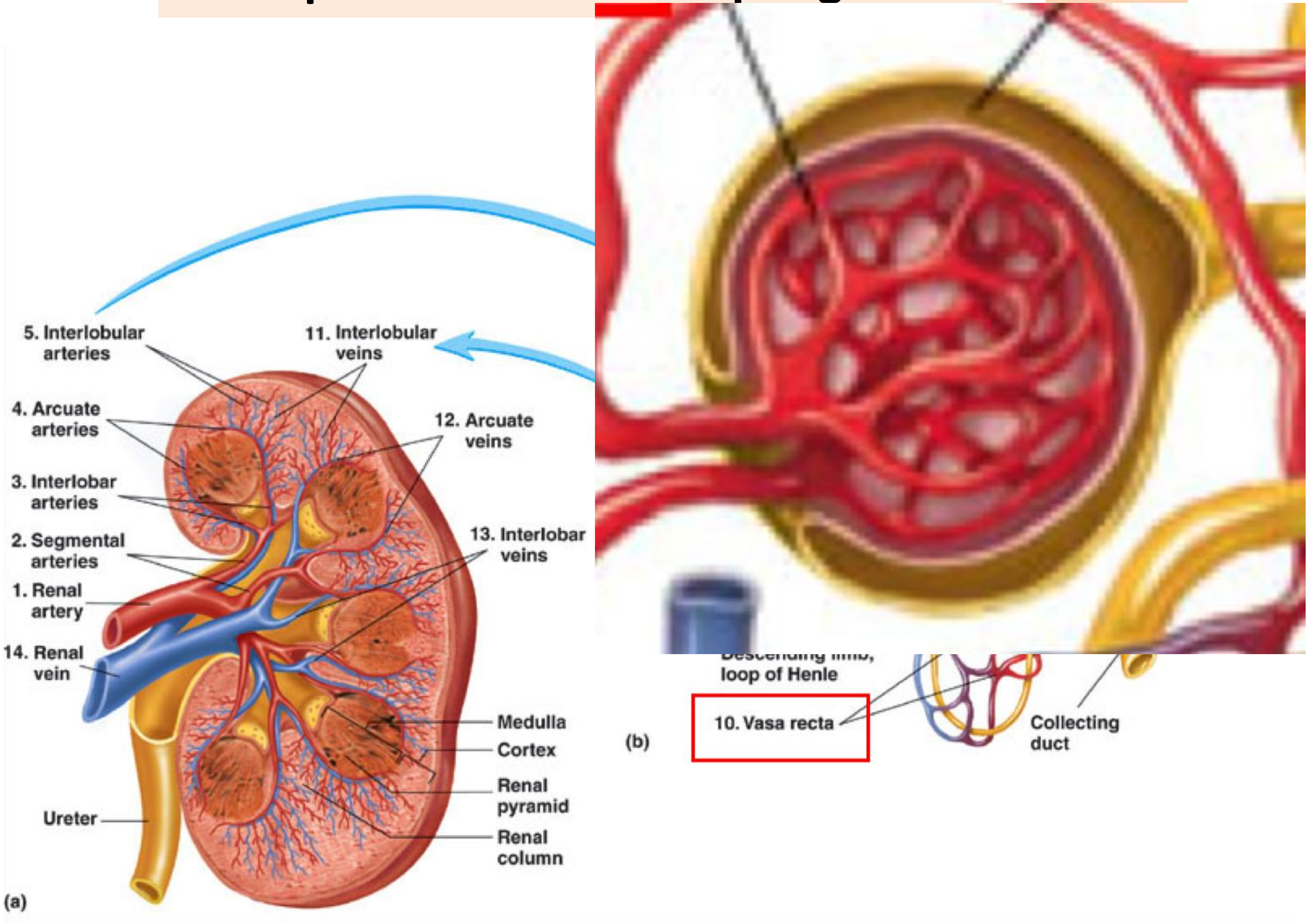
Fish gill



retinal capillaries of frog eye

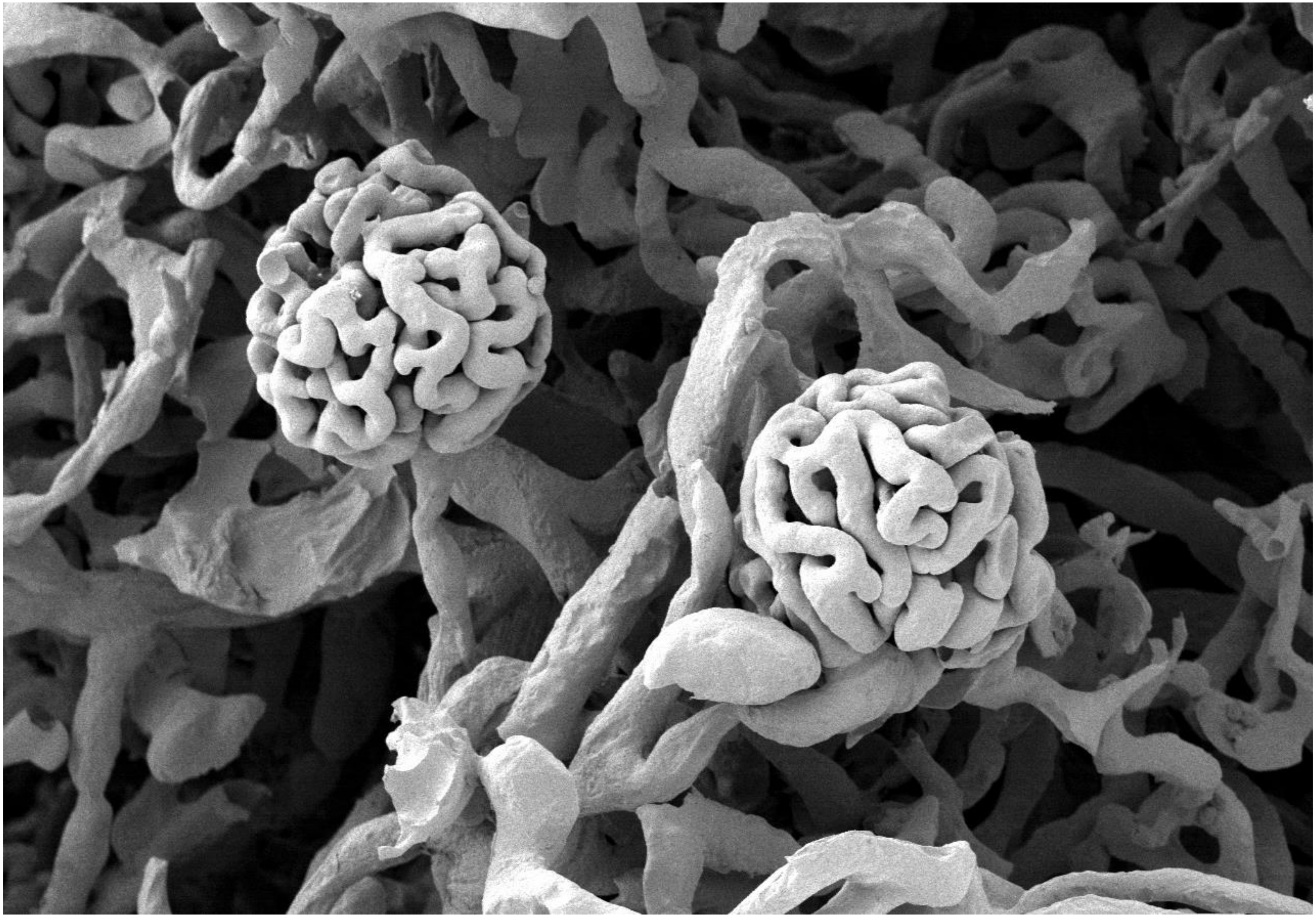
Principles of animal morphogenesis

Intro



Principles of animal morphogenesis

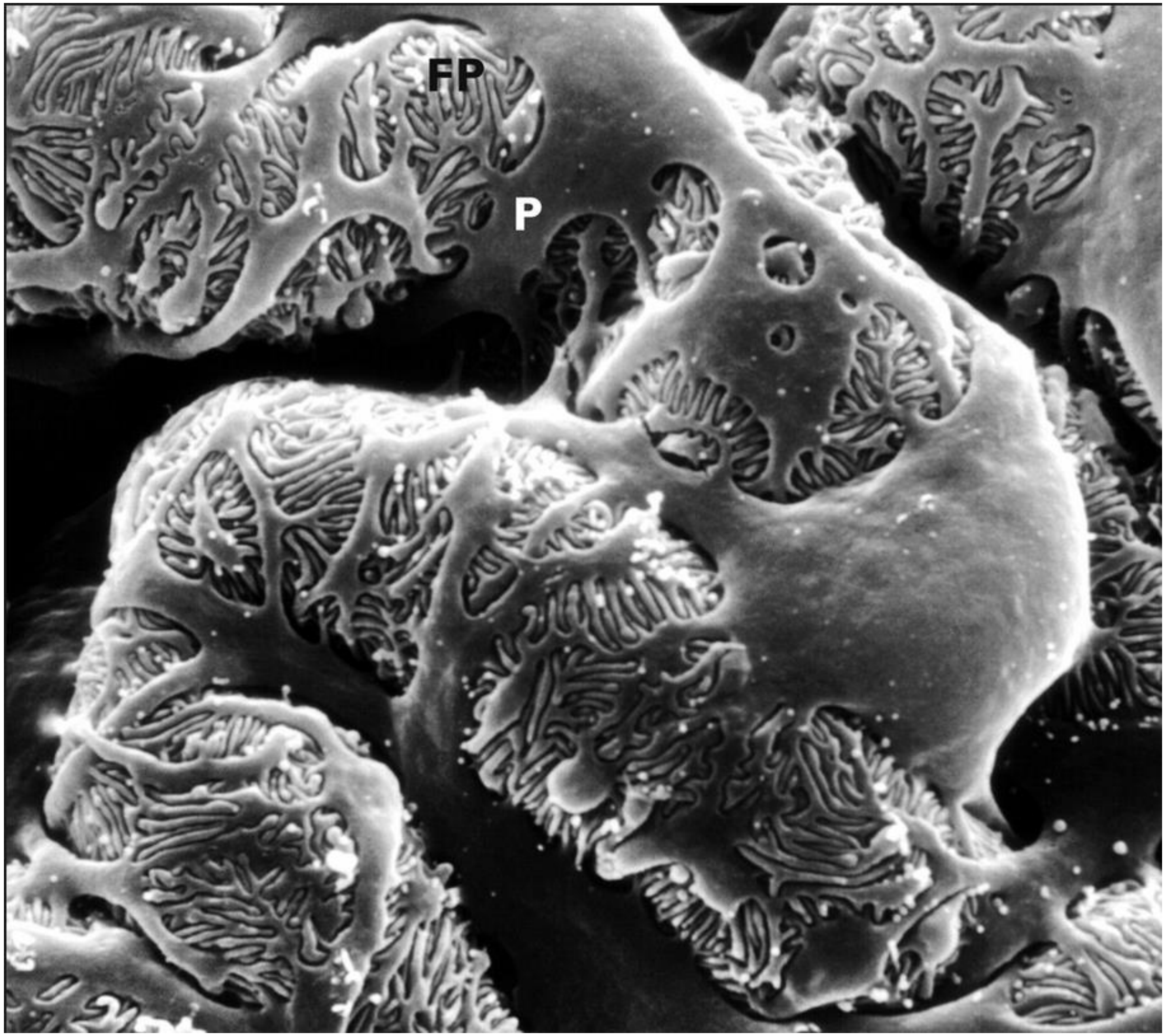
Intro



Kidney glomeruli

Principles of animal morphogenesis

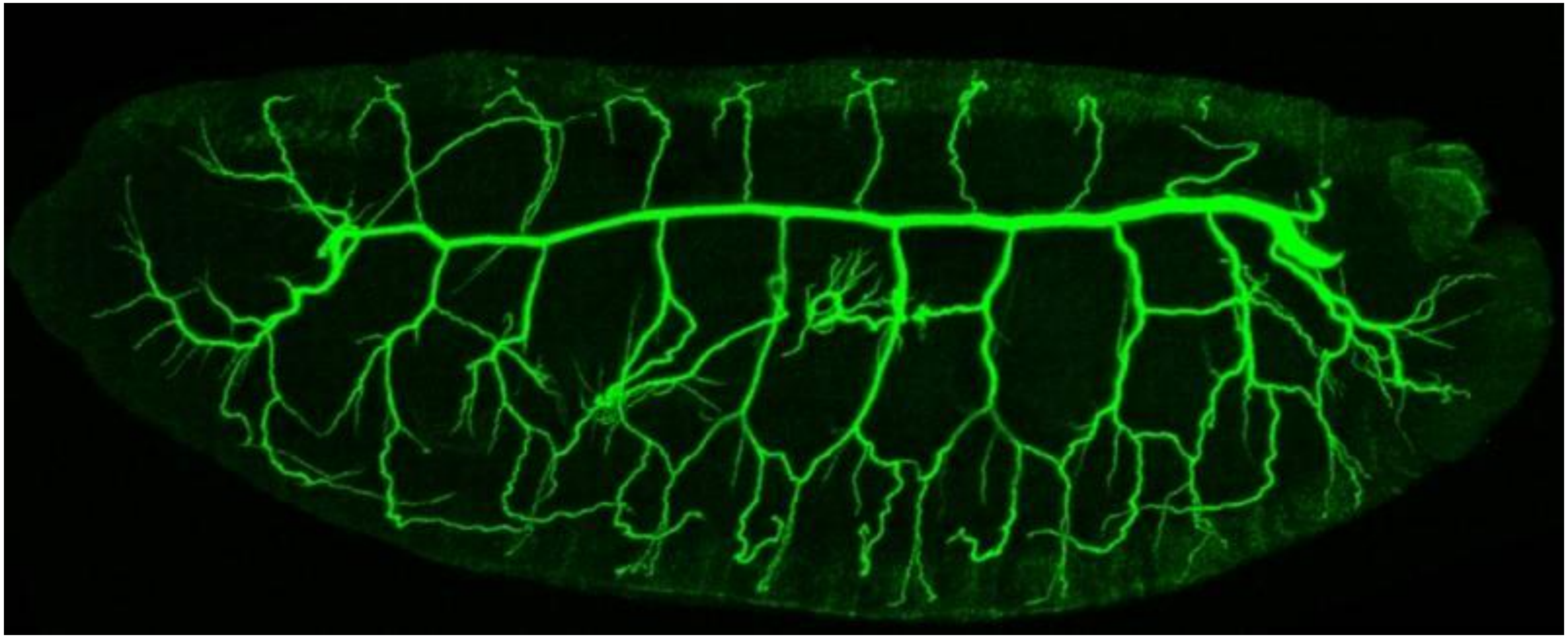
Intro



Kidney glomeruli => slits = filtration units

Principles of animal morphogenesis

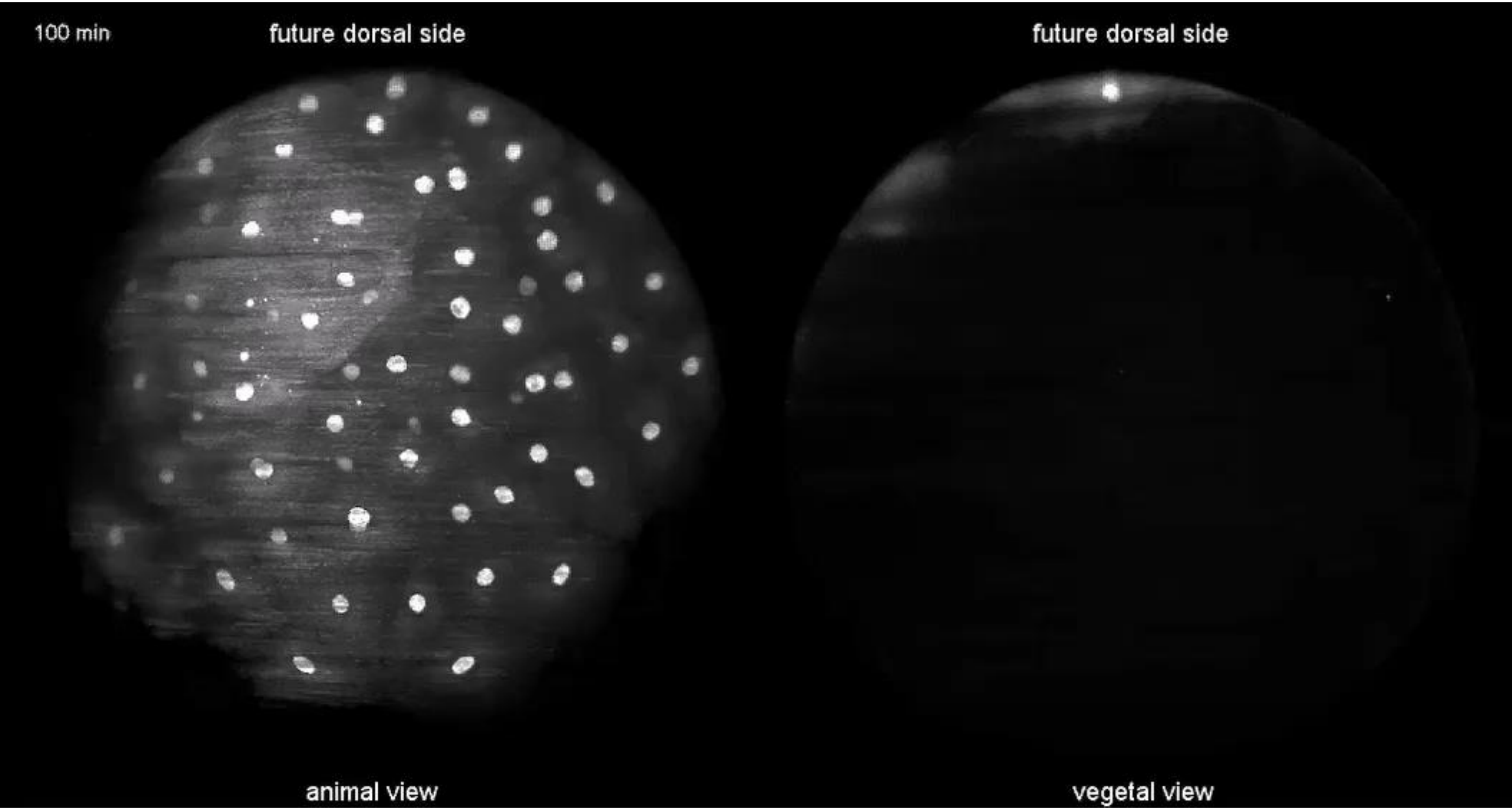
Intro



Drosophila larva tracheal system

Principles of animal morphogenesis

Intro



Zebrafish development

Keller, Schmidt, Wittbrodt, Stelzer. Science. 2008, 322:1065

Morphogenesis: a multilevel topic

Cellular
“motors”

↓

Cellular
processes

↓

Tissular
processes

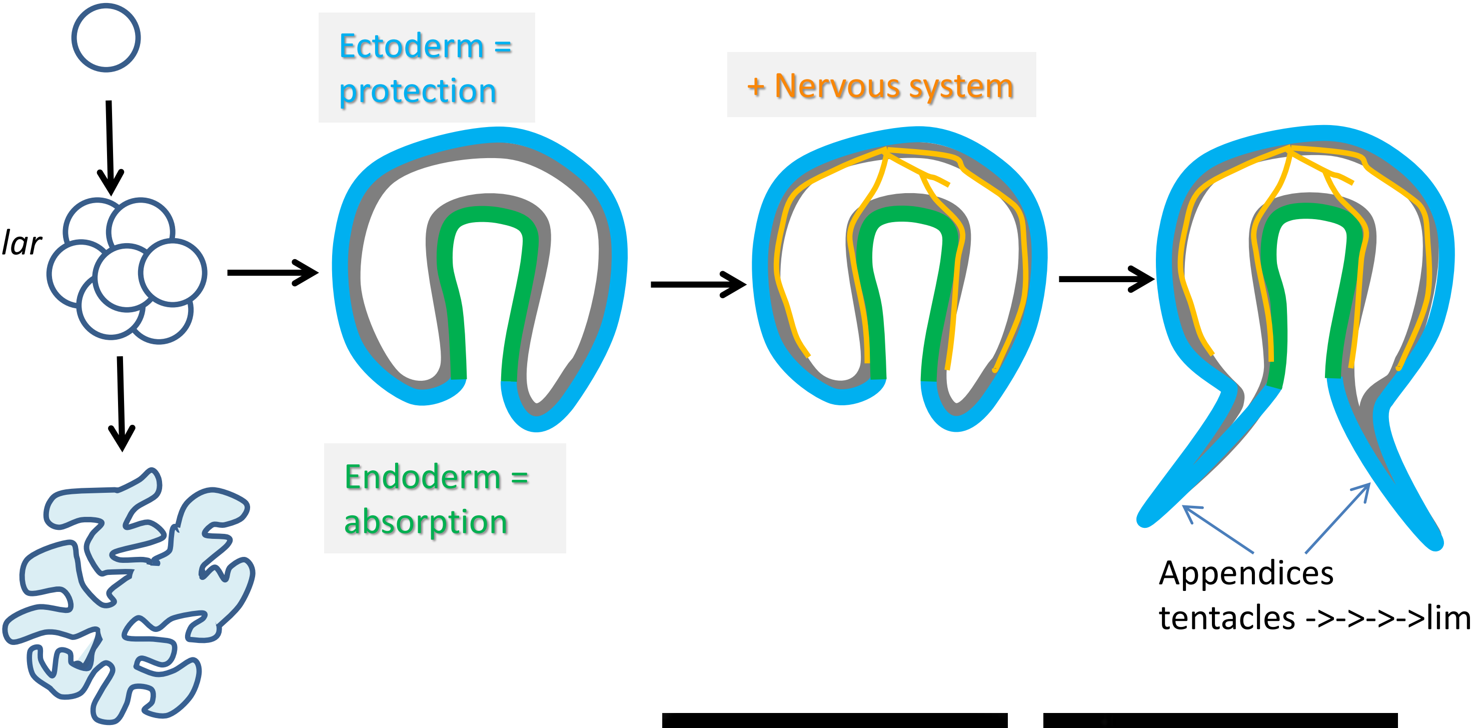
↓

Morphogenetic
events

↓

Developmental
events

First steps in metazoan morphogenesis



first multicellular “organisms”

Ectoderm = protection

+ Nervous system

Endoderm = absorption

Increased absorptive surface

Appendices
tentacles ->->->->limbs

sponges

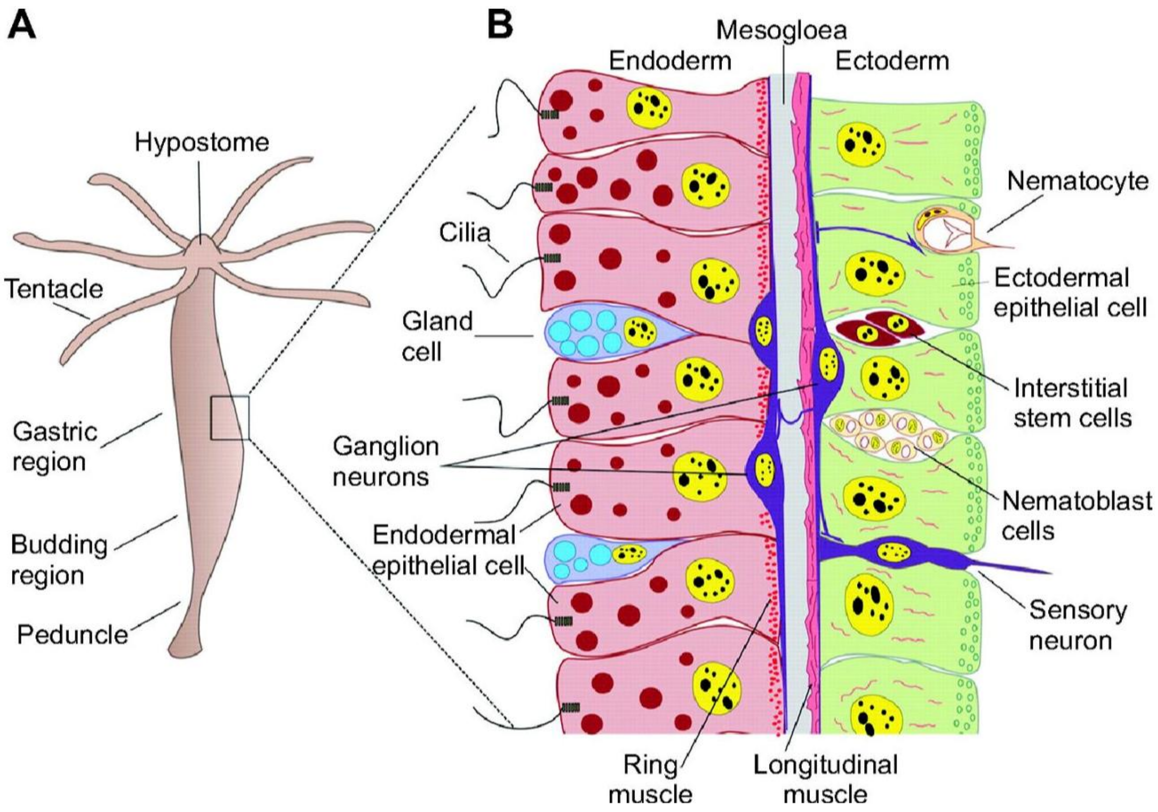
cnidaria

First steps in metazoan morphogenesis

Cnidarians = diploblastic

Ectoderm = protection

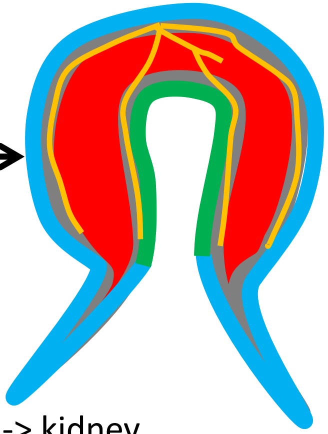
Endoderm = absorption



Journal of Experimental Biology 2015 218: 551-561; doi: 10.1242/jeb.111666

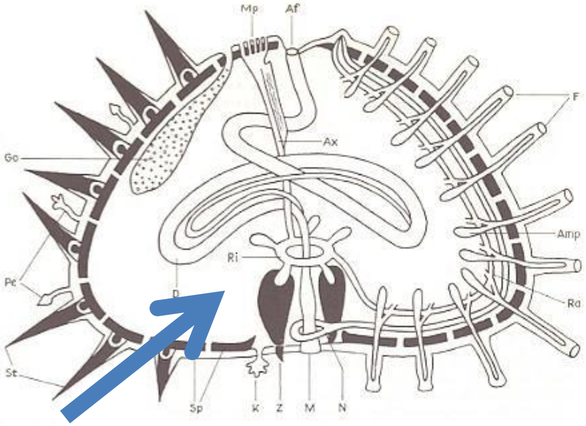
First steps in metazoan morphogenesis

Diploblastic -> Triploblastic

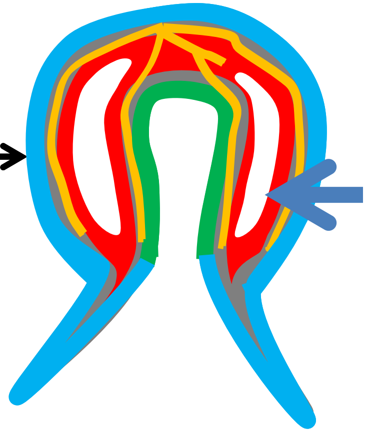


mesoderm

Mesoderm:
-> specialized contractile cells = muscle
-> specialized excretory cells – nephros -> kidney
-> internal 0_2 + nutrient circulation -> blood vessels, heart
-> defense – immune cells



Acoelomate -> Coelomate

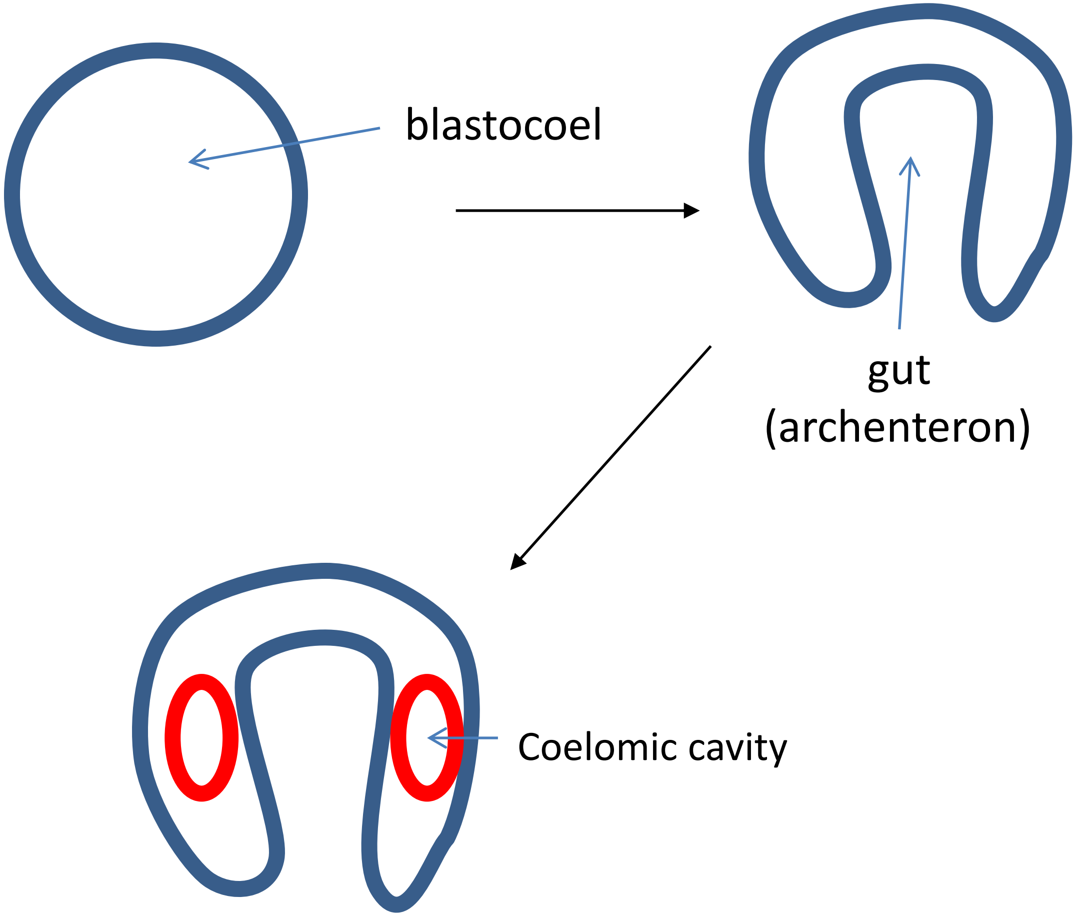


Coelomic cavity

+ Elaborated organs -> need “room” for morphogenesis (= coelom) + sophisticated movements

First steps in metazoan morphogenesis

Embryonic cavities



blastocoel

gut
(archenteron)

Coelomic cavity

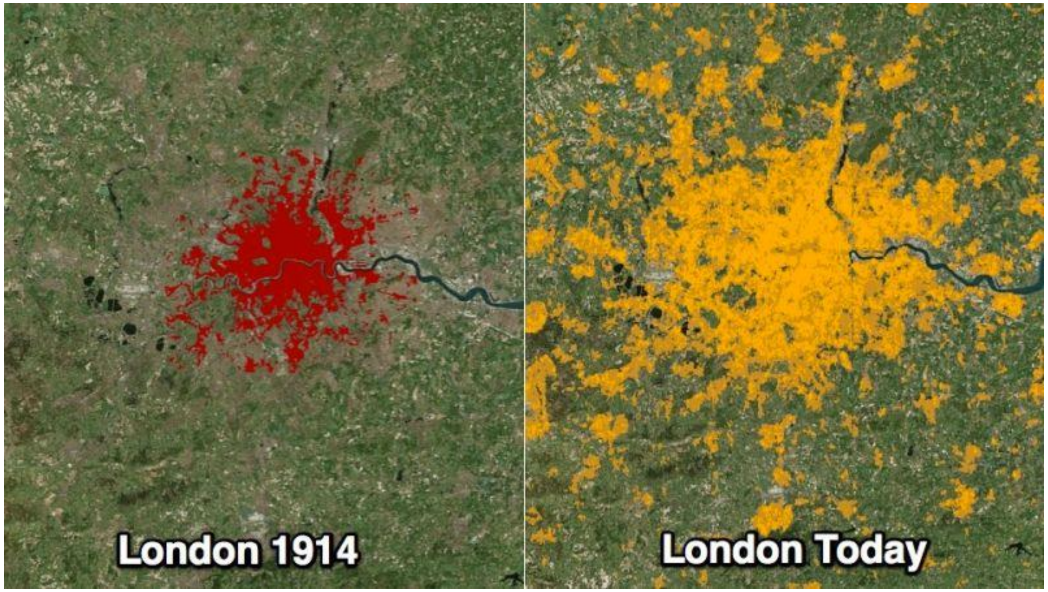
The basic cellular processes involved in morphogenesis

Cell division Apoptosis Change in cell shape Intercellular migration Cell migration

Growth
Oriented division

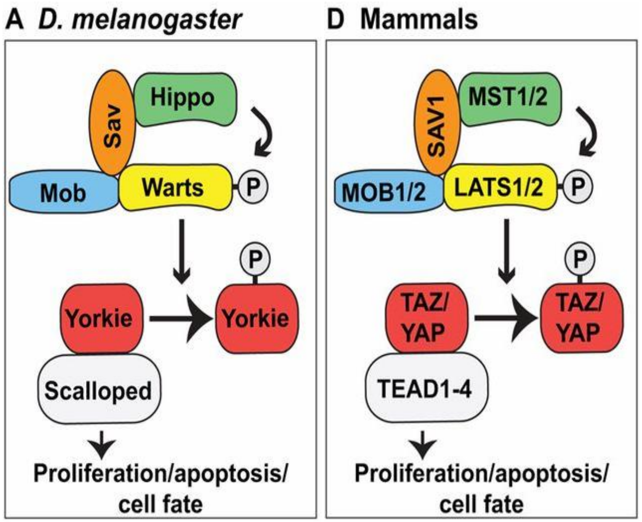
Regulation of growth

Poorly controlled growth

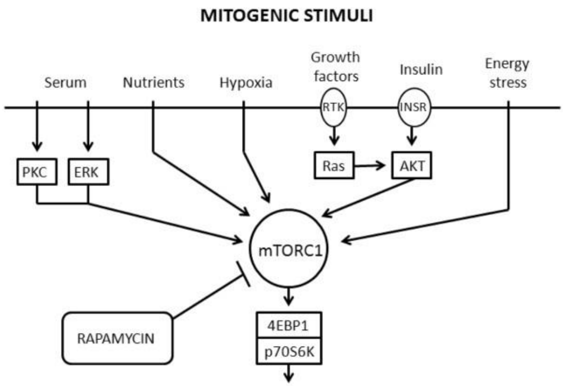


Regulation of growth

Hippo pathway



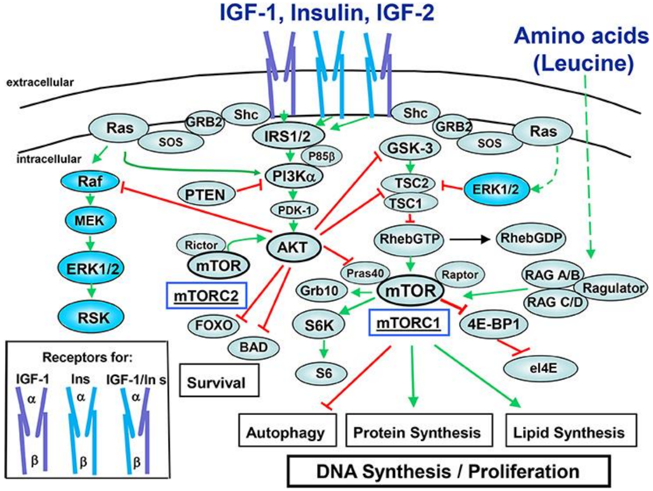
Tor pathway



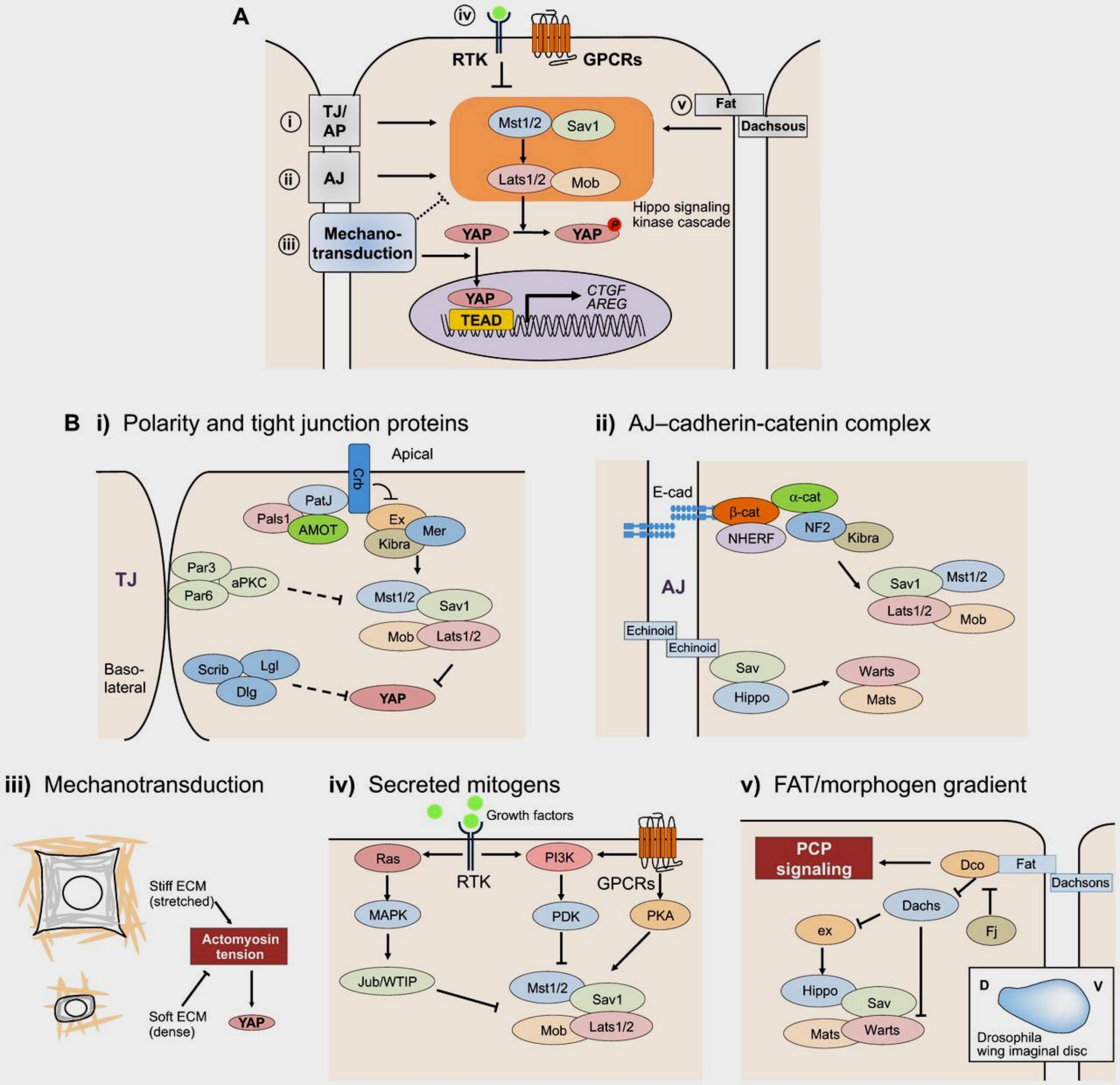
Translation of proteins

↓

Cell survival
Cell growth/ proliferation
Ion channel expression
Neurogenesis
Axonal sprouting



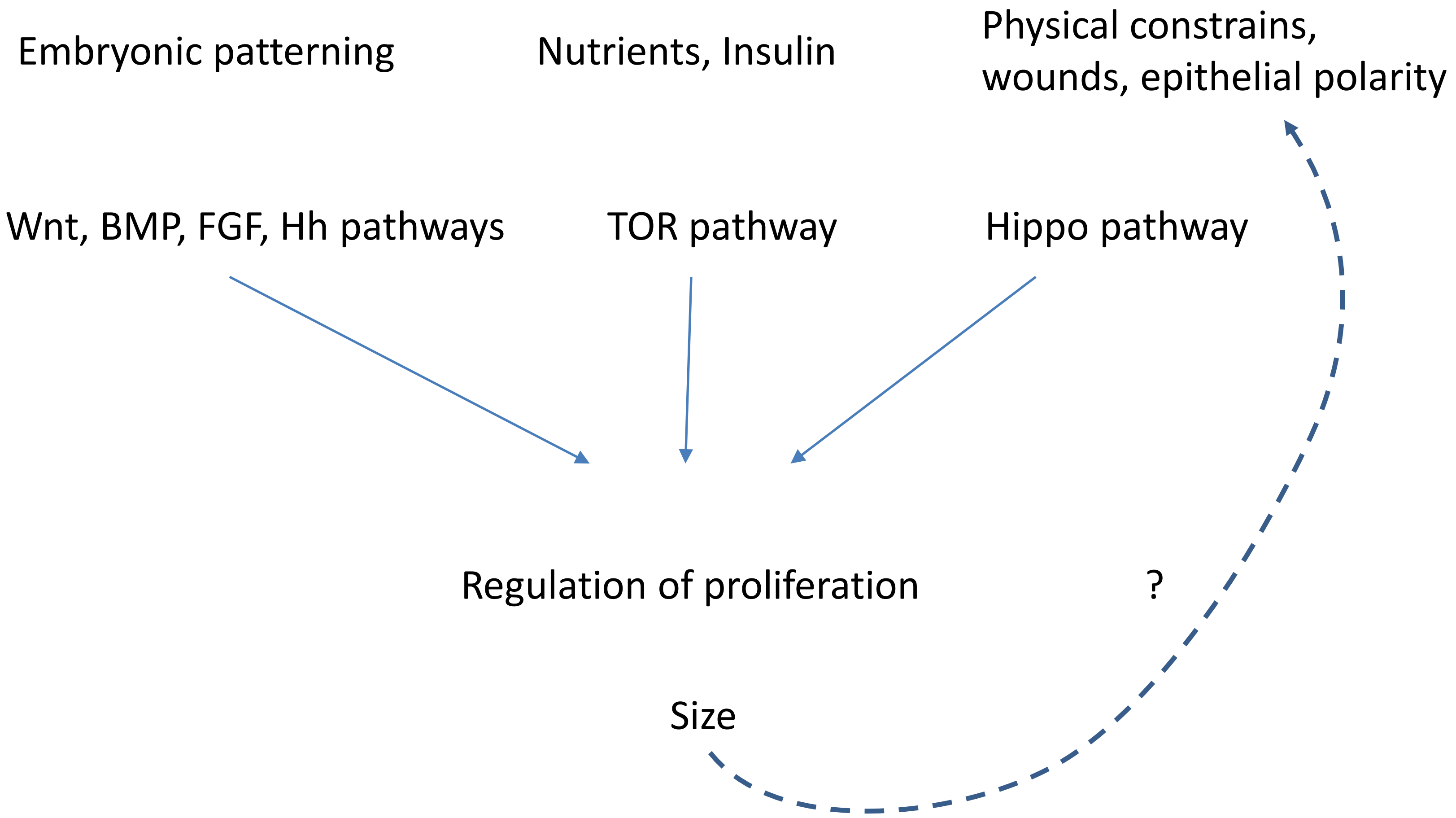
Control of the core Hippo signaling pathway through interacting upstream modules.



Barry M. Gumbiner, and Nam-Gyun Kim J Cell Sci 2014;127:709-717

Control of the core Hippo signaling pathway through interacting upstream modules. (A) Overview of the interactions of various modules with the core pathway. The Hippo pathway consists of a core kinase cascade in which the transcriptional co-activators YAP/TAZ are phosphorylated and inactivated by either their exclusion from the nucleus or their enhanced degradation. The nuclear activity of YAP/TAZ promotes cell growth. (B) Upstream modules. (Panels i, ii) Two upstream cell surface regulators, epithelial polarity or tight junction (TJ) complexes (i) and adherens junction (AJ) or cadherin–catenin complexes may function together to sense the integrity of the epithelial layer. (Panel iii) Cell shape and mechanotransduction can regulate the activity of YAP/TAZ independently of Lats kinase, but Lats-dependent regulation of YAP/TAZ through the actin cytoskeleton has also been observed. (Panel iv) Extracellular soluble growth factors act reciprocally – with contact inhibition – through the Hippo pathway to integrate mitogenesis with growth inhibitory mechanisms. (Panel v) The atypical cadherins FAT and Dachsous set up a morphogen gradient to control the spatial patterning of both cell proliferation (through Hippo pathway signaling) and PCP. β-cat, β-catenin; α-cat, α-catenin, AP, apical polarity complexes; Dco, Discs overgrown; E-cad, E-cadherin; ECM, extracellular matrix; ex, Expanded; GPCRs, G-protein-coupled receptors; RTK, receptor tyrosine kinase; PCP, planar cell polarity.

Regulation of growth



Embryonic patterning

Nutrients, Insulin

Physical constrains,
wounds, epithelial polarity

Wnt, BMP, FGF, Hh pathways

TOR pathway

Hippo pathway

Regulation of proliferation

?

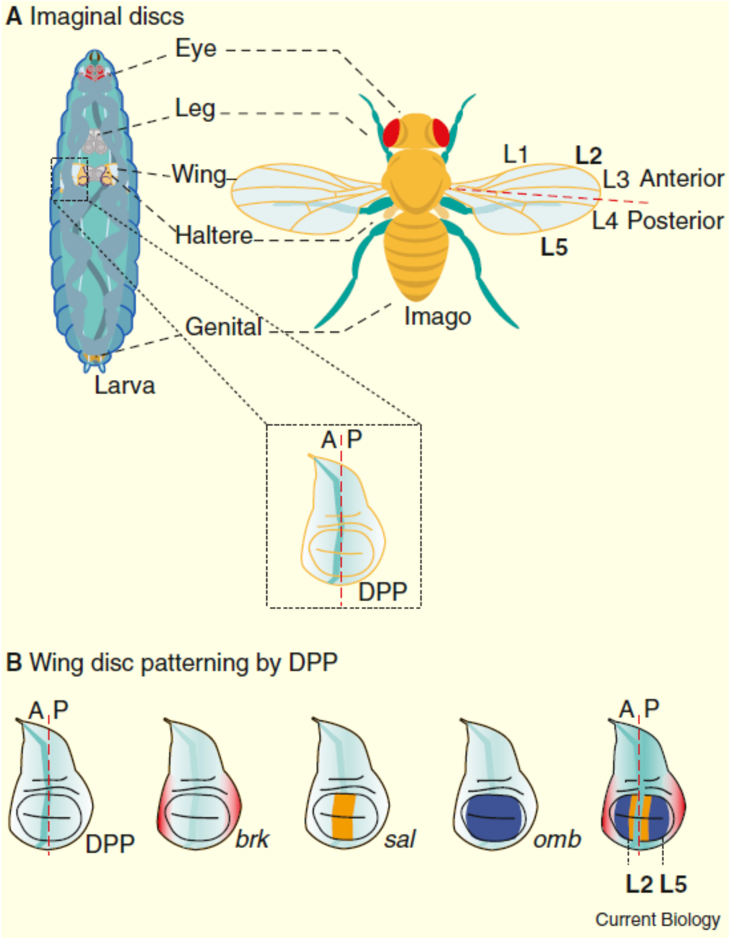
Size

Experimental model to study regulation of growth: Drosophila larval imaginal discs

Current Biology 24, R245–R255, March 17, 2014 ©2014 Elsevier Ltd All rights reserved http://dx.doi.org/10.1016/j.cub.2014.01.055

Coordination of Patterning and Growth by the Morphogen DPP

Simon Restrepo[1,#], Jeremiah J. Zartman[2,#], and Konrad Basler[1,*]



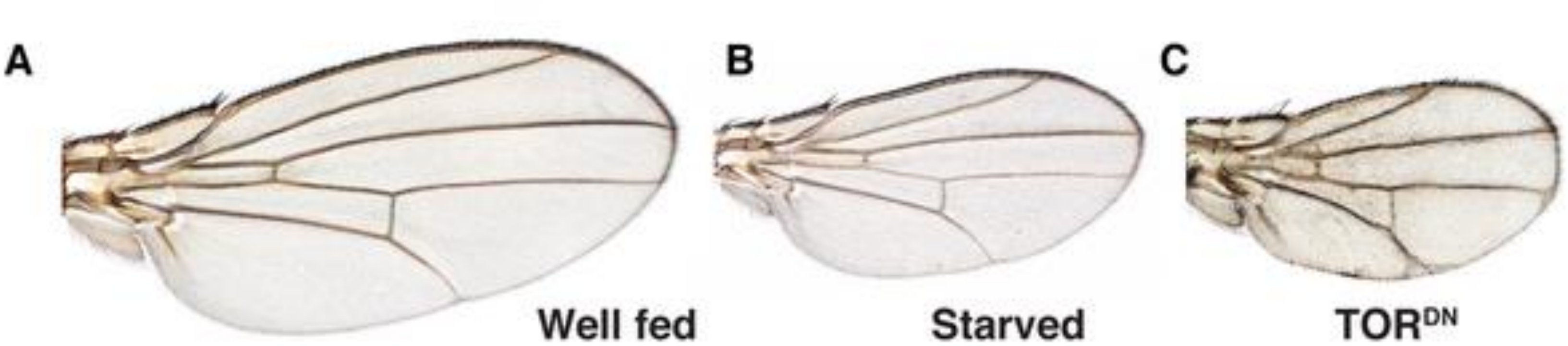
Current Biology

Dpp = Decapentaplegic = BMP
Brk = brinker (TF)

Figure 1. Imaginal discs and DPP-mediated patterning.
(A) Imaginal discs are primordial structures of adult insect appendages that are already present at the larval stage. During metamorphosis each imaginal disc develops into a specific adult appendage (eye, wing, leg, genital, etc.). Drosophila imaginal discs undergo patterning and growth during the larval stages. Imaginal discs are constituted of approximately 50 cells during the first larval instar and will grow up to 50,000 cells before the onset of pupation. The larval stage depicted is late 3rd instar. (B) The DPP pathway patterns the wing disc along the A-P axis. DPP diffuses from a thin stripe of cells at the center of the disc and represses the expression of brk. The resultant activity of DPP and BRK leads to the nested expression domains of sal and omb. The domain boundaries of sal and omb will correspond to anatomical landmarks in the adult wing such as the position of the wing veins (L2 and L5).

Growth regulation: Integration of various inputs

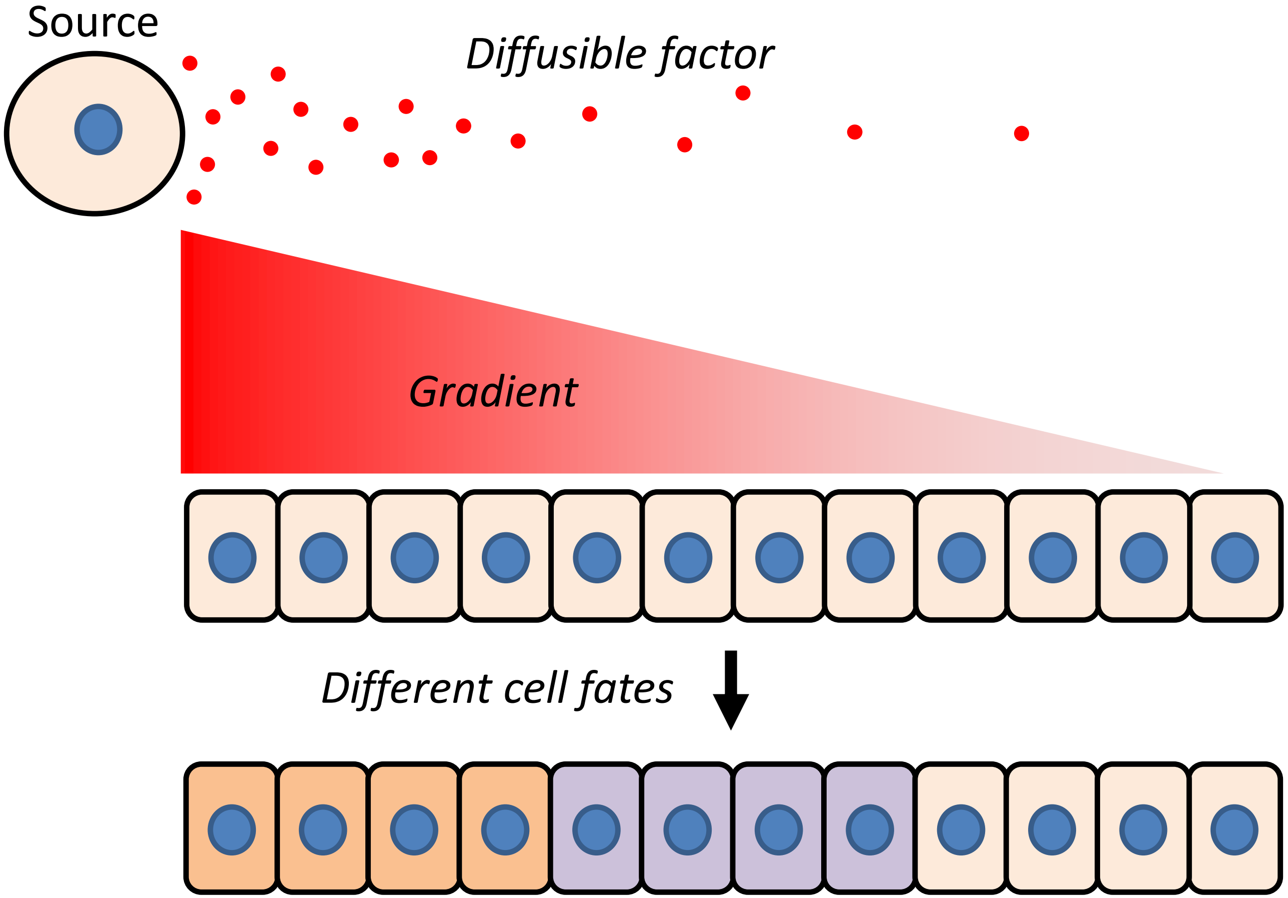
Effects of TOR inhibition on wing growth



Parker J, Struhl G (2015) Scaling the Drosophila Wing: TOR-Dependent Target Gene Access by the Hippo Pathway Transducer Yorkie. PLOS Biology 13(10): e1002274. doi:10.1371/journal.pbio.1002274
http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002274

Growth: scaling and maintenance of patterns

Morphogens



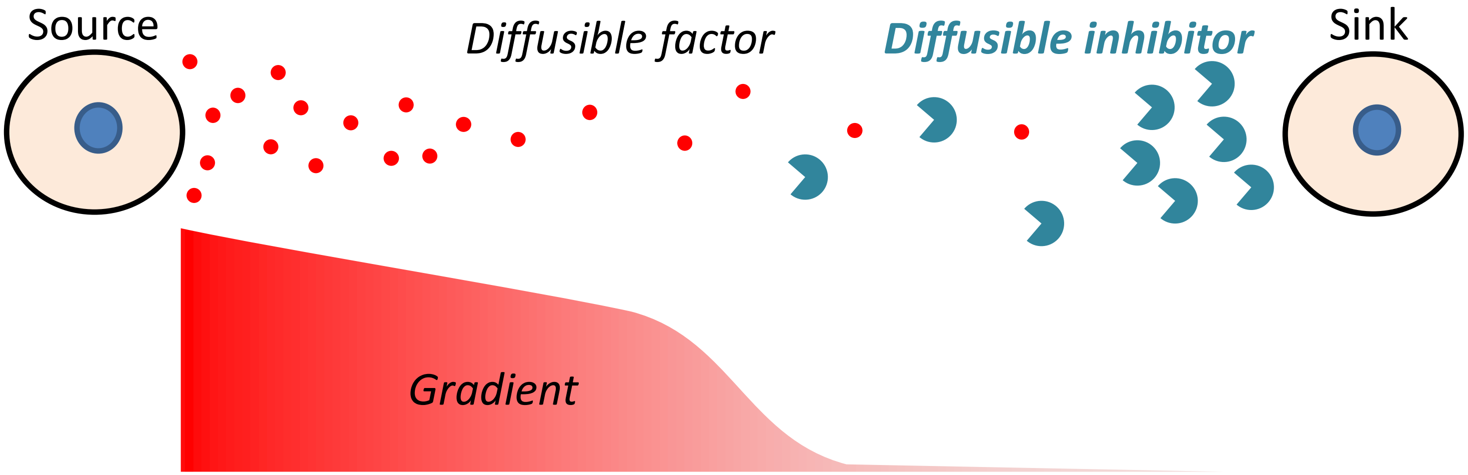
Source

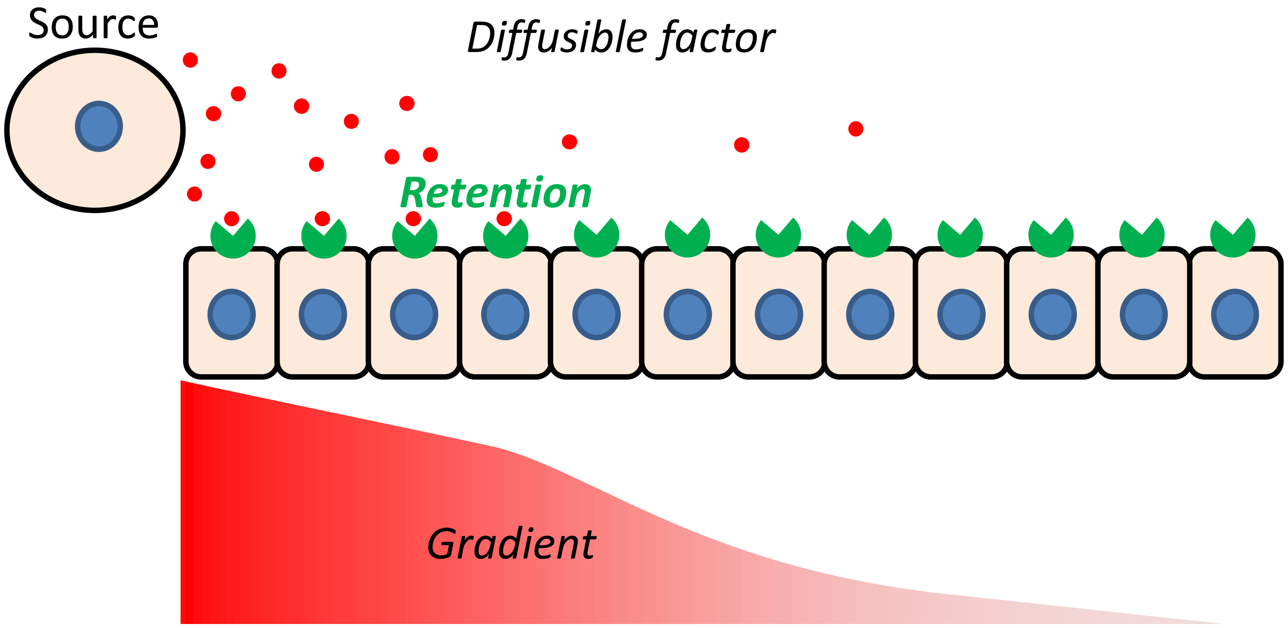
Diffusible factor

Gradient

Different cell fates

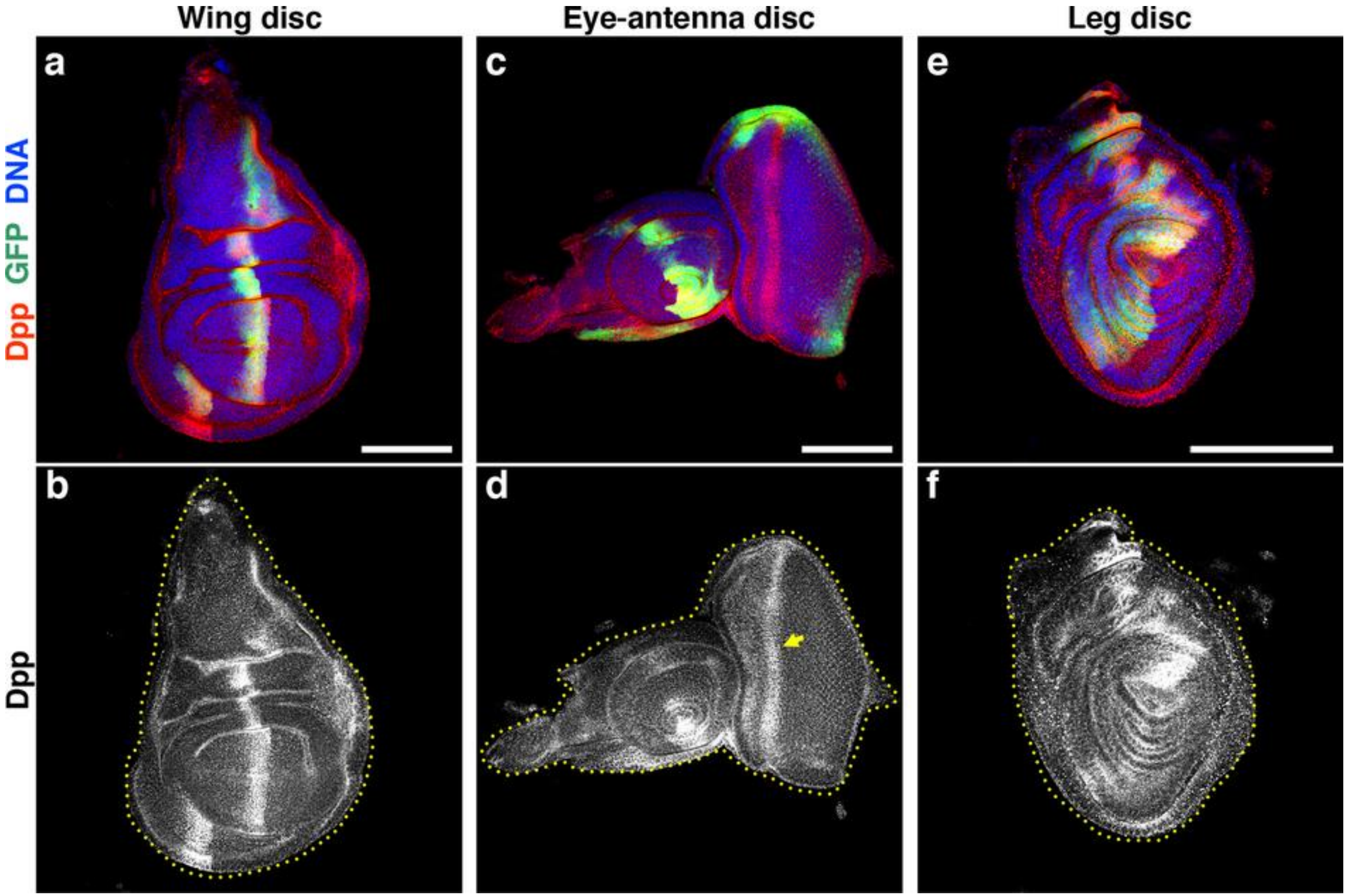
Morphogens: Examples of various types of gradients





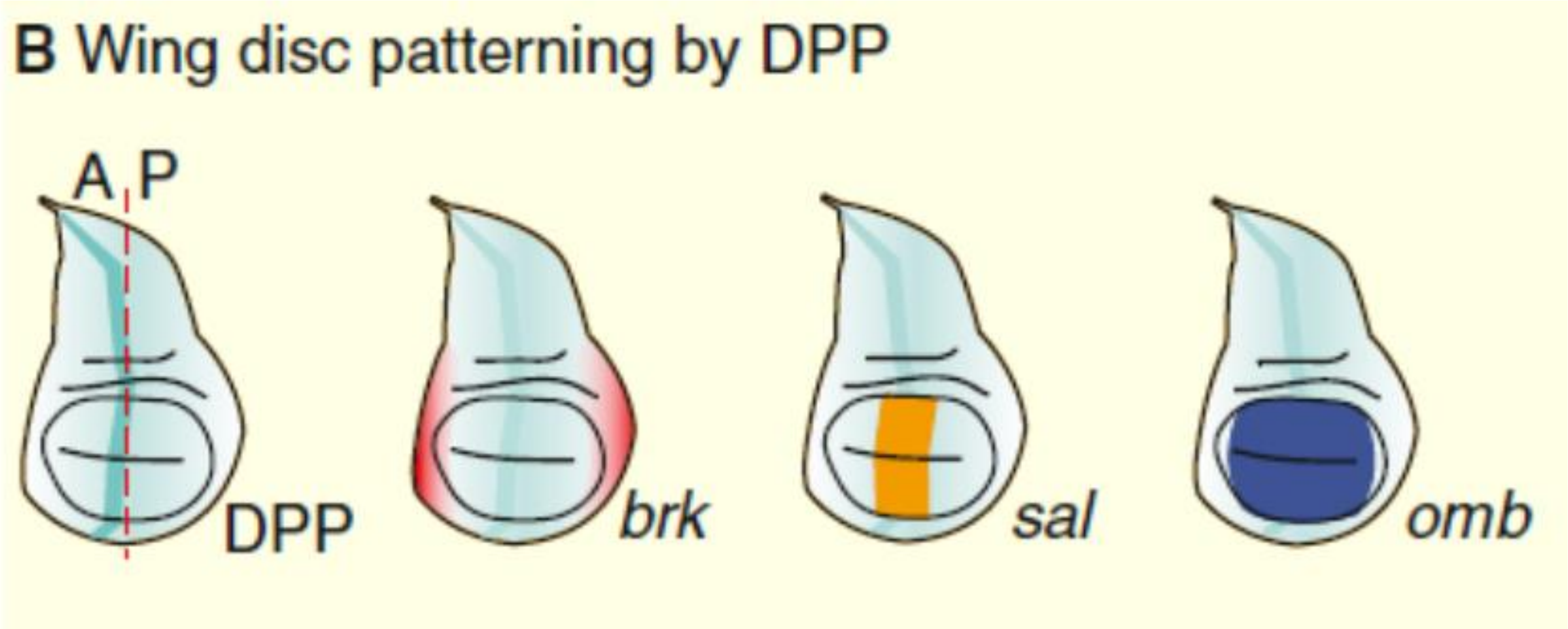
Example: Dpp (BMP) and controlled growth of Drosophila larval imaginal discs

Decapentaplegic and growth control in the developing Drosophila wing
Takuya Akiyama & Matthew C. Gibson
Nature 527, 375–378 (19 November 2015) doi:10.1038/nature15730



a–**f**, Wing (**a**, **b**), eye–antenna (**c**, **d**), and leg (**e**, **f**) imaginal discs from *UAS-GFP/+; dpp-GAL4/+* larvae are dissected and stained with anti-Dpp antibody. GFP (green) indicates *dpp-GAL4*-expressing cells. Note that *dpp-GAL4* is not expressed in the morphogenetic furrow of the third instar eye–antenna disc (arrow in **d**). Dotted lines show outlines of imaginal discs. Blue: DNA. Scale bars, 100 µm. Anterior is left.

Example: Dpp (BMP) and controlled growth of Drosophila larval imaginal discs



Dpp ⊣ brk

Example: Dpp (BMP) and controlled growth of Drosophila larval imaginal discs

The problem of scaling

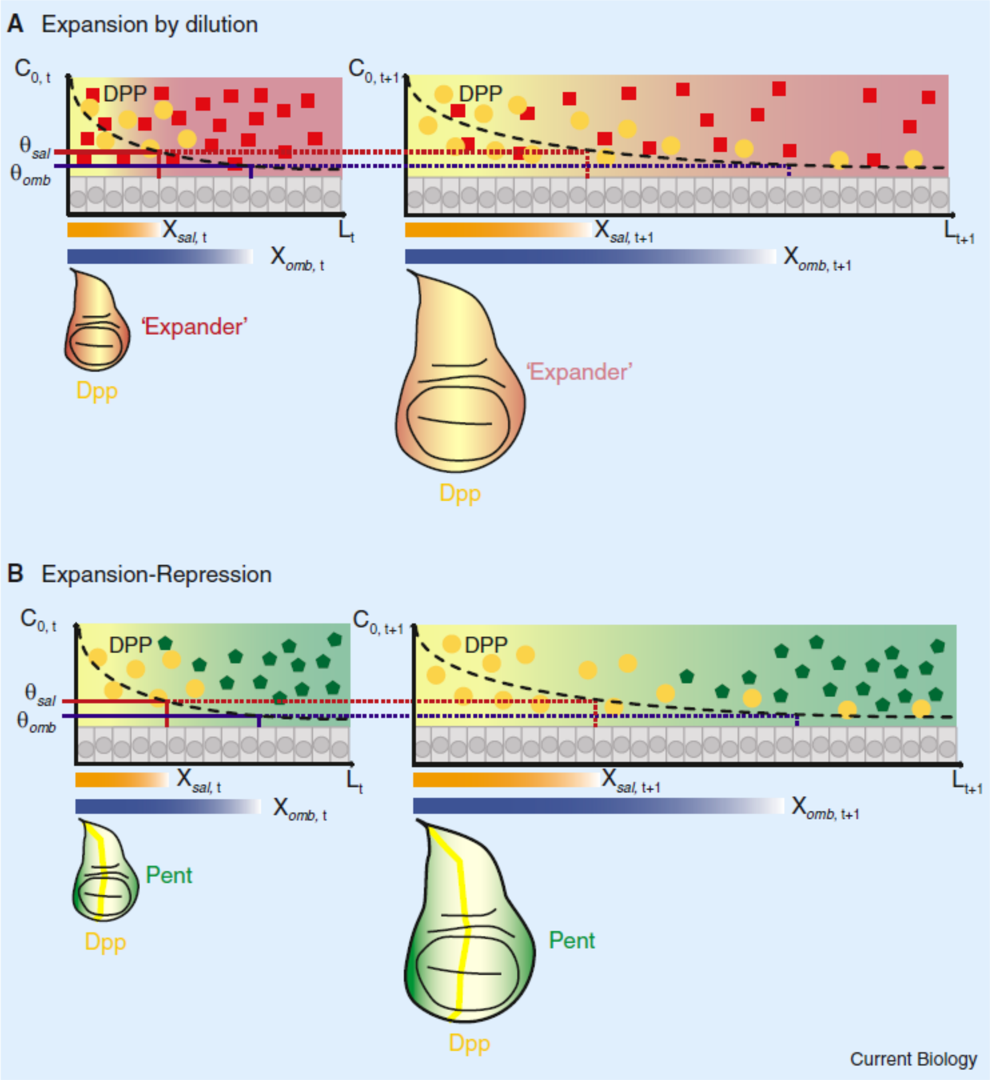
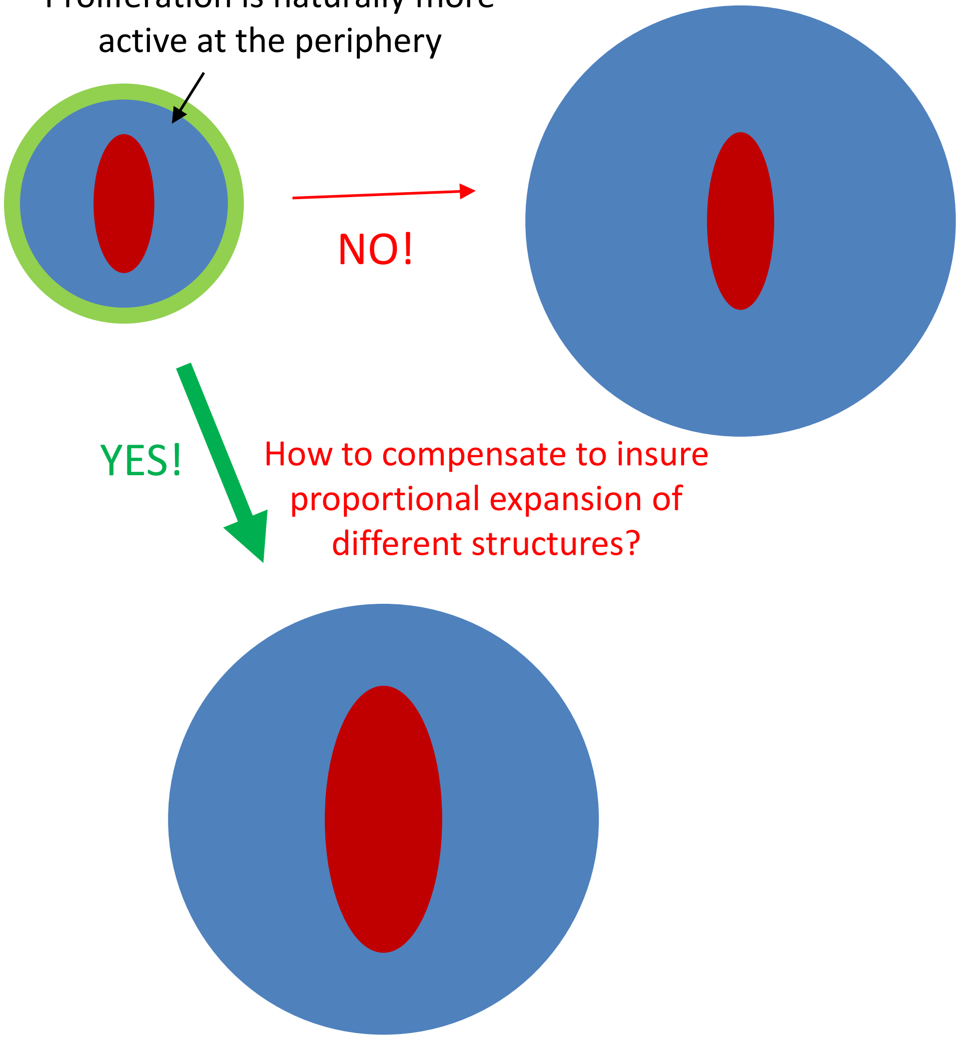


Figure 6. Scaling models.
(A) Expansion by dilution: a long-lived antagonist promotes DPP degradation and thus hinders its dispersion. However, growth dilutes the antagonist such that as the disc area increases, DPP movement is facilitated. In this way the DPP gradient can expand further as the disc grows.
(B) Expansion-repression: An expander, PENT facilitates DPP diffusion but PENT expression is repressed by DPP. Initially DPP does not reach the expression domain of PENT, thus PENT is actively produced and diffuses through the wing disc. As PENT increases DPP diffusion, DPP starts to repress pent expression and the concentration of the
expander decreases accordingly.

Current Biology 24, R245–R255, March 17, 2014

How to grow in ‘harmony’?



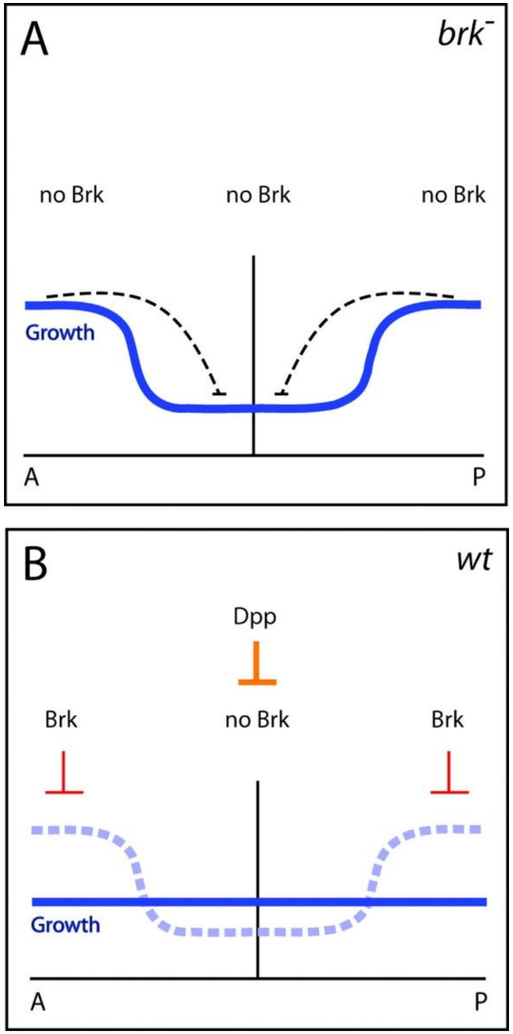
Proliferation is naturally more active at the periphery

NO!

YES!

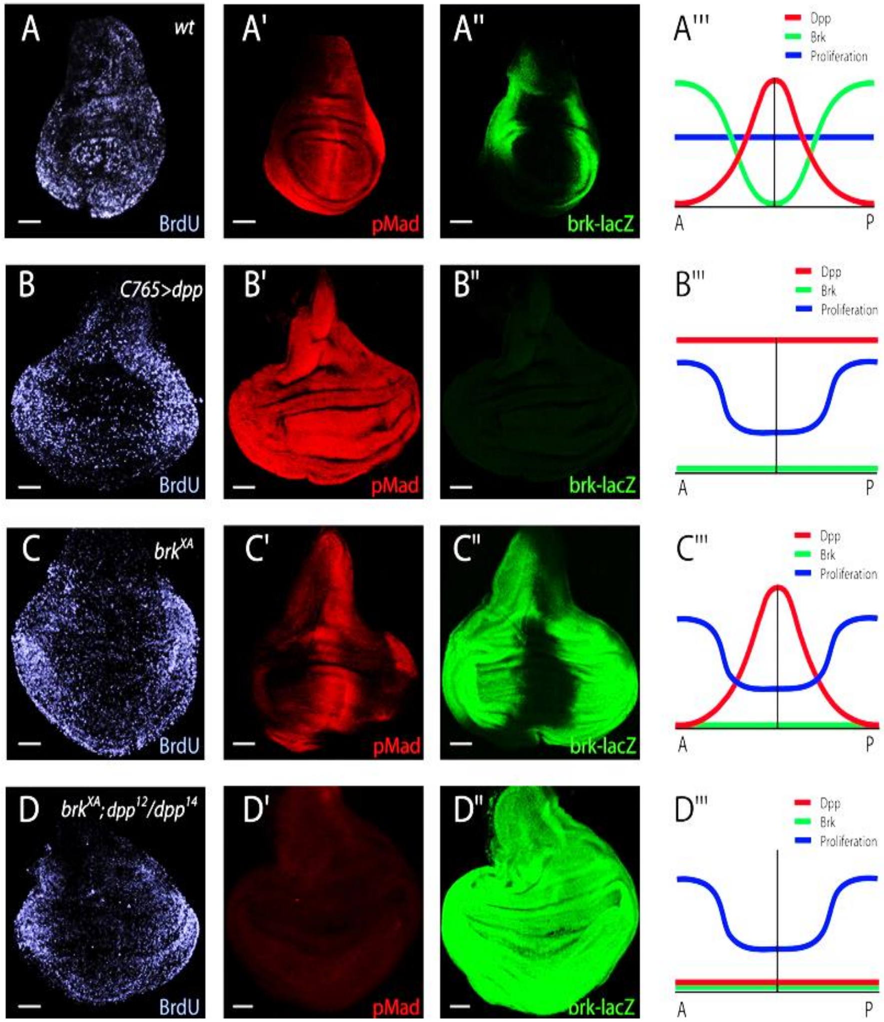
How to compensate to insure proportional expansion of different structures?

Model of growth regulation in Drosophila wing discs by the Dpp-Brk system.



Gerald Schwank et al. Development 2008;135:4003-4013

Comparison of cell proliferation, disc size and Dpp signaling activity between wild-type discs and discs with altered brk levels or Dpp pathway activity.



BrdU

Mad(Smad)

Brk reporter

wt

dpp GOF

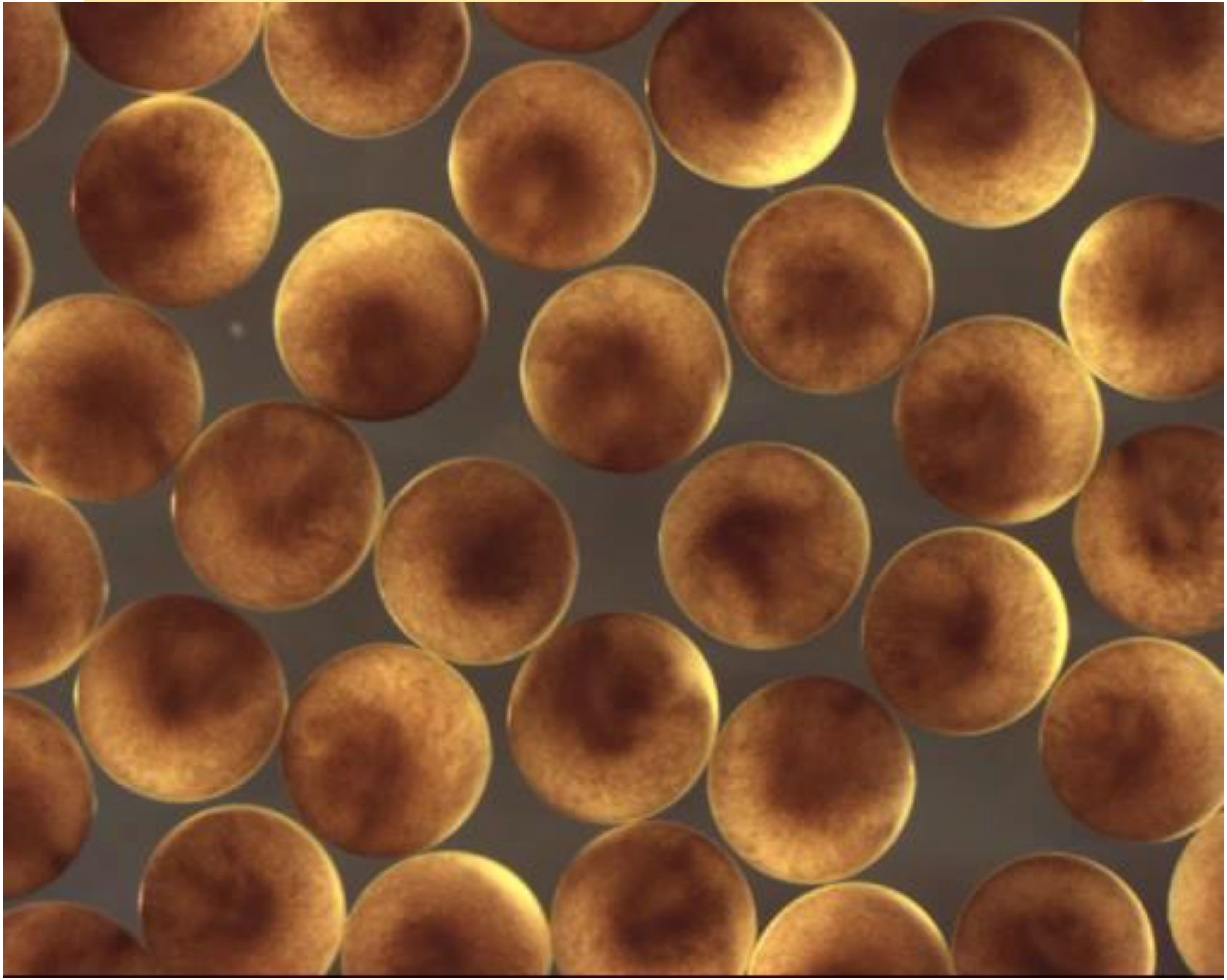
brk LOF

brk+Dpp LOF

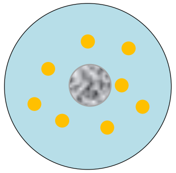
Gerald Schwank et al. Development 2008;135:4003-4013

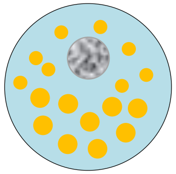
Cell division: Cleavage

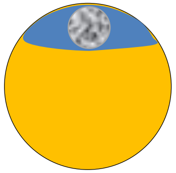
Example of cleavage: Xenopus (amphibian)

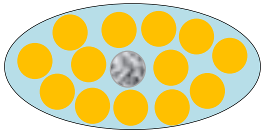


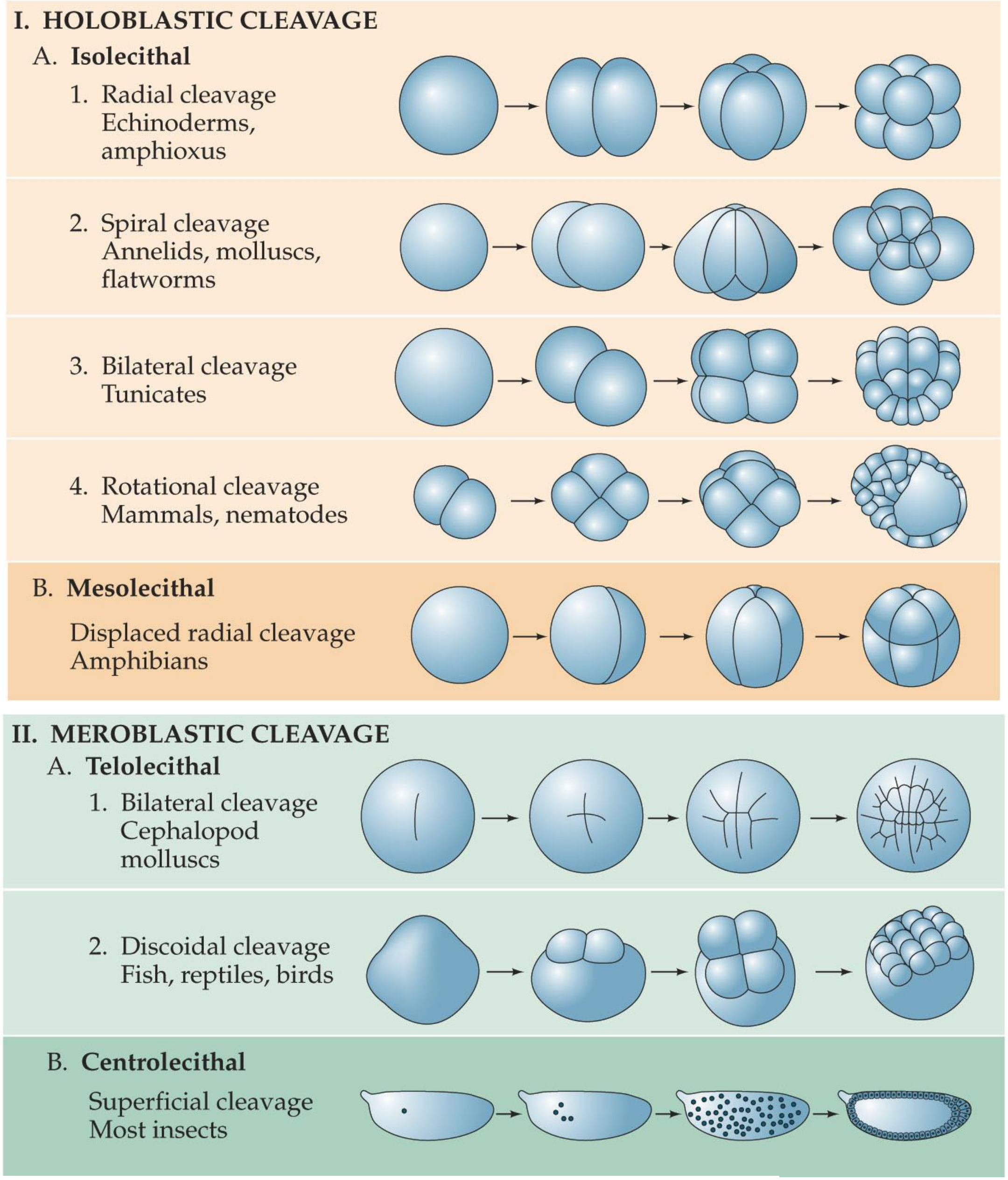
Early embryo development – Types of cleavage





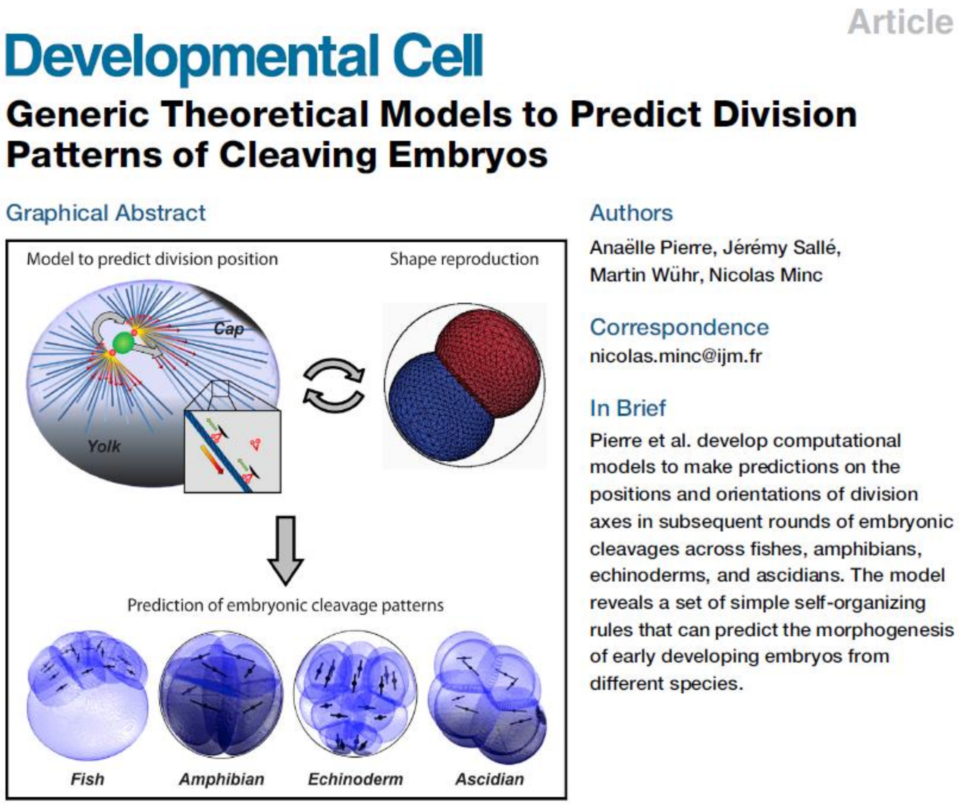






DEVELOPMENTAL BIOLOGY, Eighth Edition, Figure 8.3 (Part 2) © 2006 Sinauer Associates, Inc.

Early embryo development – Modelling cleavage



Article

Developmental Cell

Generic Theoretical Models to Predict Division Patterns of Cleaving Embryos

Graphical Abstract

Authors

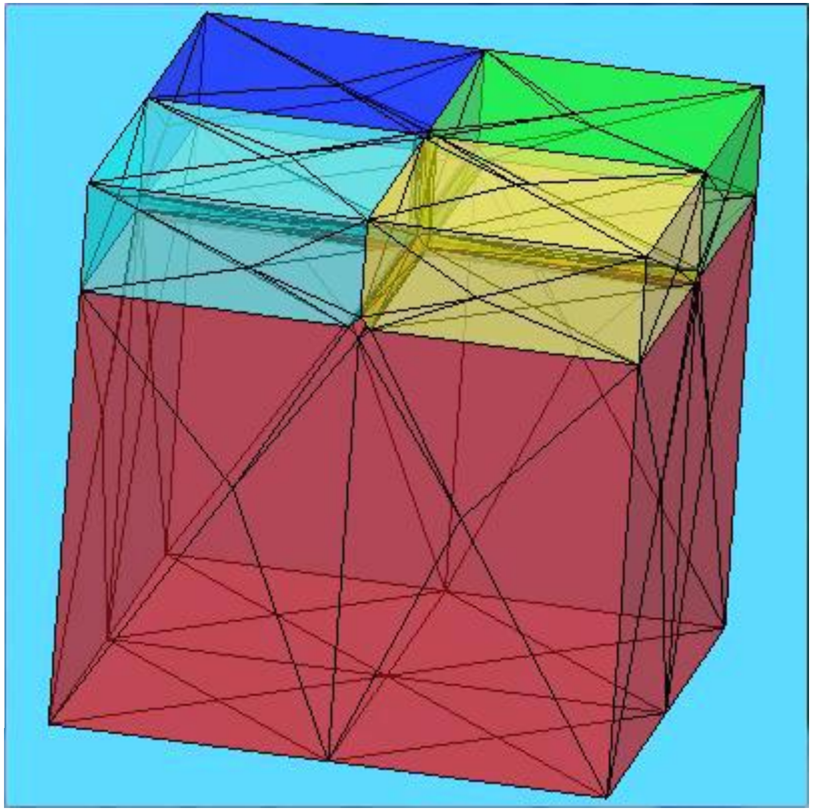
Anaëlle Pierre, Jérémy Sallé,
Martin Wühr, Nicolas Minc

Correspondence

nicolas.minc@ijm.fr

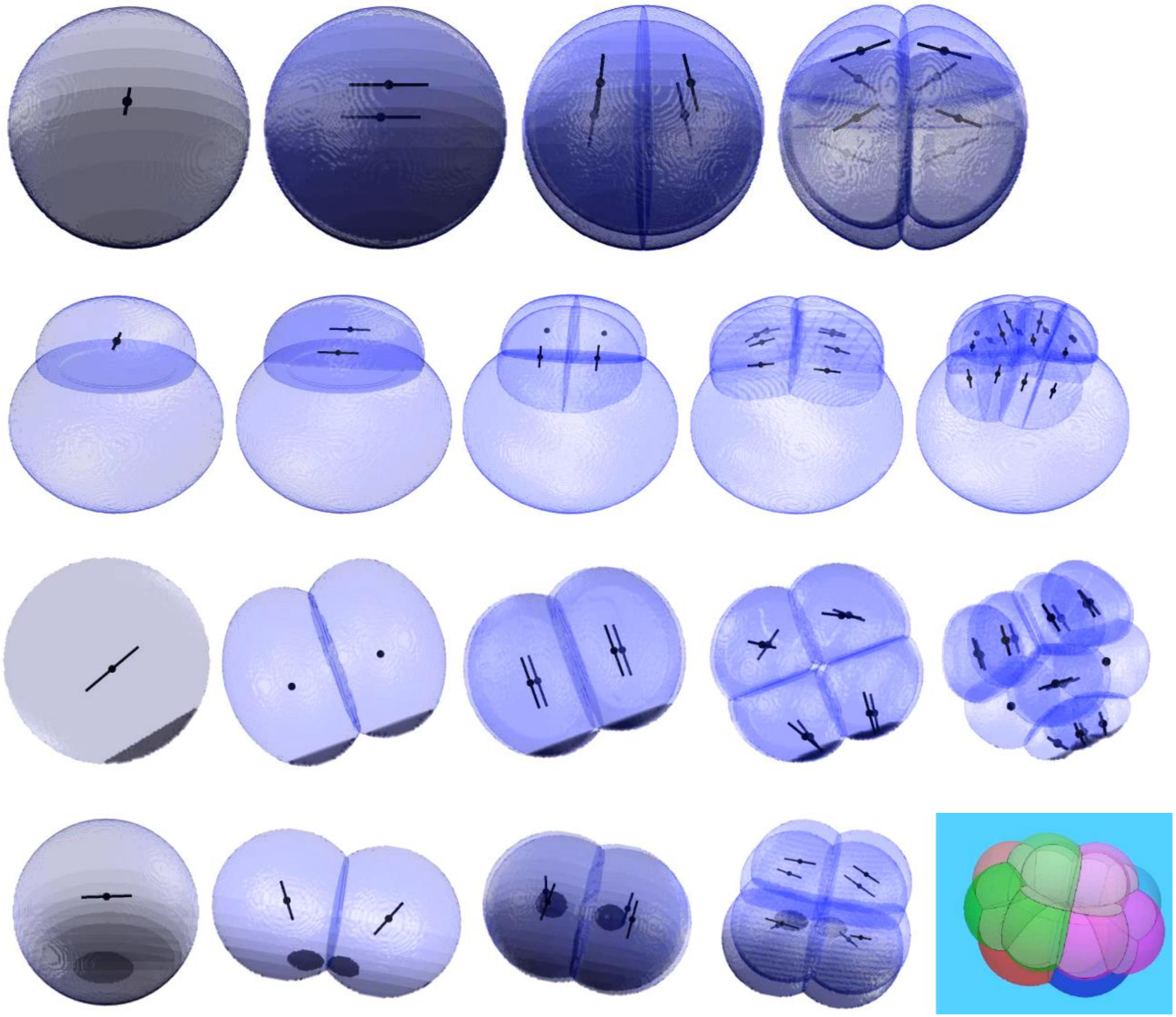
In Brief

Pierre et al. develop computational models to make predictions on the positions and orientations of division axes in subsequent rounds of embryonic cleavages across fishes, amphibians, echinoderms, and ascidians. The model reveals a set of simple self-organizing rules that can predict the morphogenesis of early developing embryos from different species.

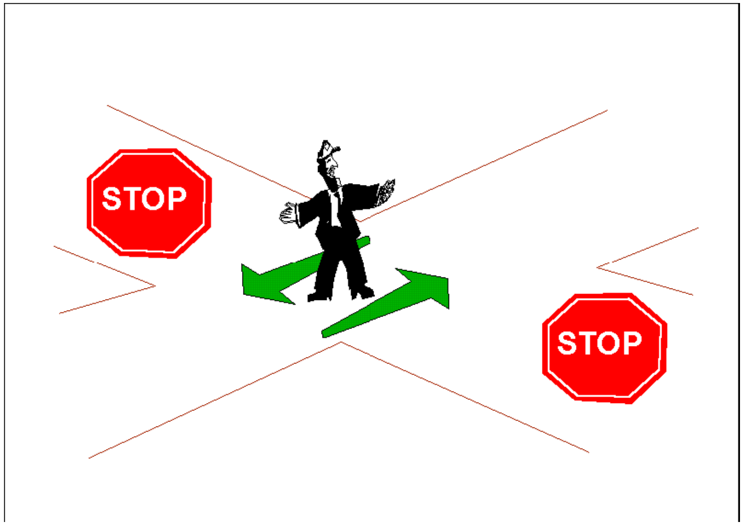


Pierre et al., 2016, Developmental Cell 39, 667–682

Early embryo development – Modelling cleavage



Oriented cell division



Oriented cell division

Current Biology Vol 15 No 18
R758

Dispatches

Organ Shape: Controlling Oriented Cell Division

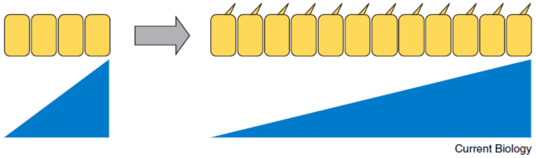


Figure 1. Control of organ size and cell polarity by gradient signals.
Growth within a tissue could be controlled by reference to a gradient signal (blue). Cell growth and proliferation remains active as long as the steepness of the gradient exceeds a certain threshold level (left). Once the slope of the gradient falls below a threshold due to continued growth, cell growth and proliferation are arrested (right). The same gradient signal could also be used by cells to determine their polarity, shown in this example by production of hairs on each cell which point up the gradient.

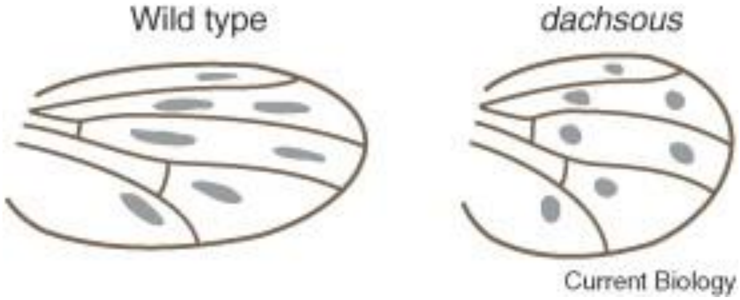


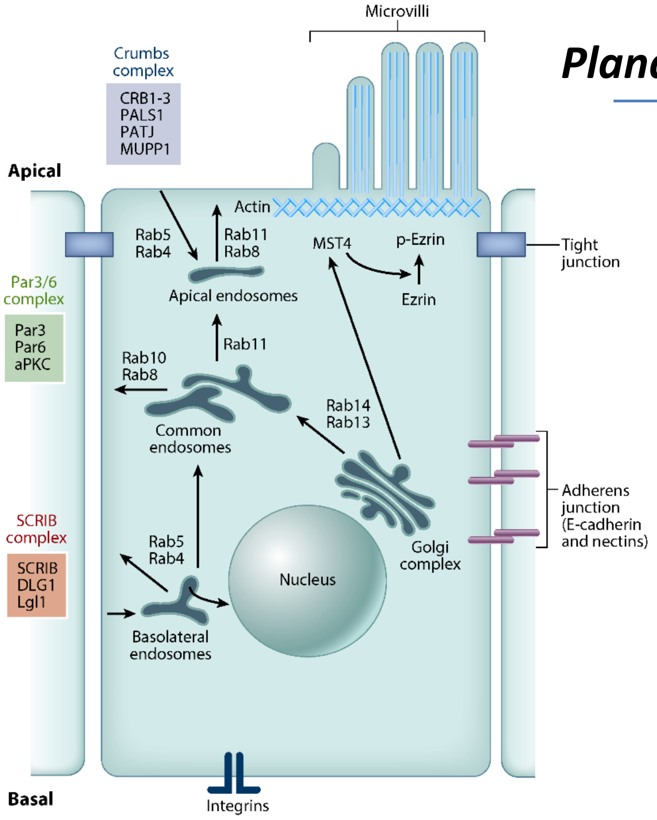
Figure 2.
Abnormal wing shape in Drosophila dachsous mutants.
During wild-type wing development (left) cell divisions are preferentially oriented on the proximodistal axis (left to right in diagram), producing clones of cells elongated on this axis and contributing to formation of a longer narrower wing. In wings lacking dachsous activity (right), cell divisions are no longer oriented on the proximodistal axis, resulting in clones that are less elongated and a shorter wing. Note that clones of cells lacking ds are also more rounded with smoother edges than clones of wild-type cells, due to a difference in cell adhesion [16], which may also contribute to the shortening of the wing. The relative contributions of the effects of loss of oriented cell divisions and changes in cell adhesion are currently unknown.

Baena-López, L.A., Baonza, A., and García-Bellido, A. (2005). The orientation of cell divisions determines the shape of *Drosophila* organs. Curr. Biol., in press.

Epithelial polarity (polarities)

Planar Cell Polarity

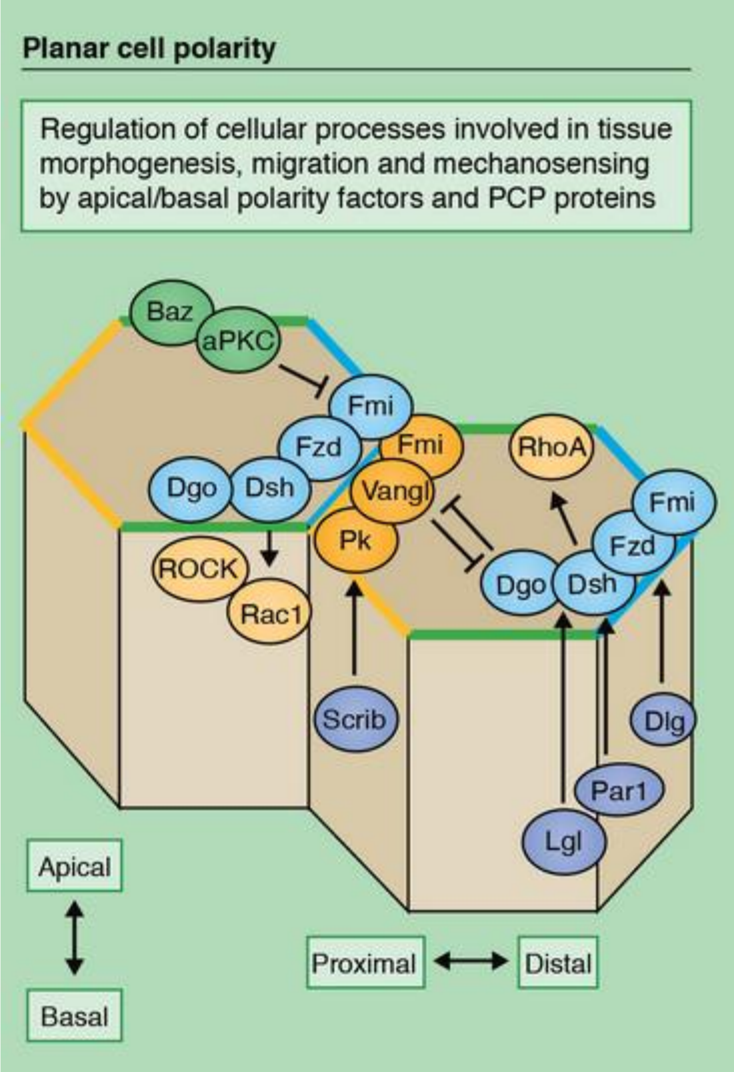
Apical Basolateral Polarity



Blasky AJ, et al. 2015.
Annu. Rev. Cell Dev. Biol. 31:575–91

Annual Reviews

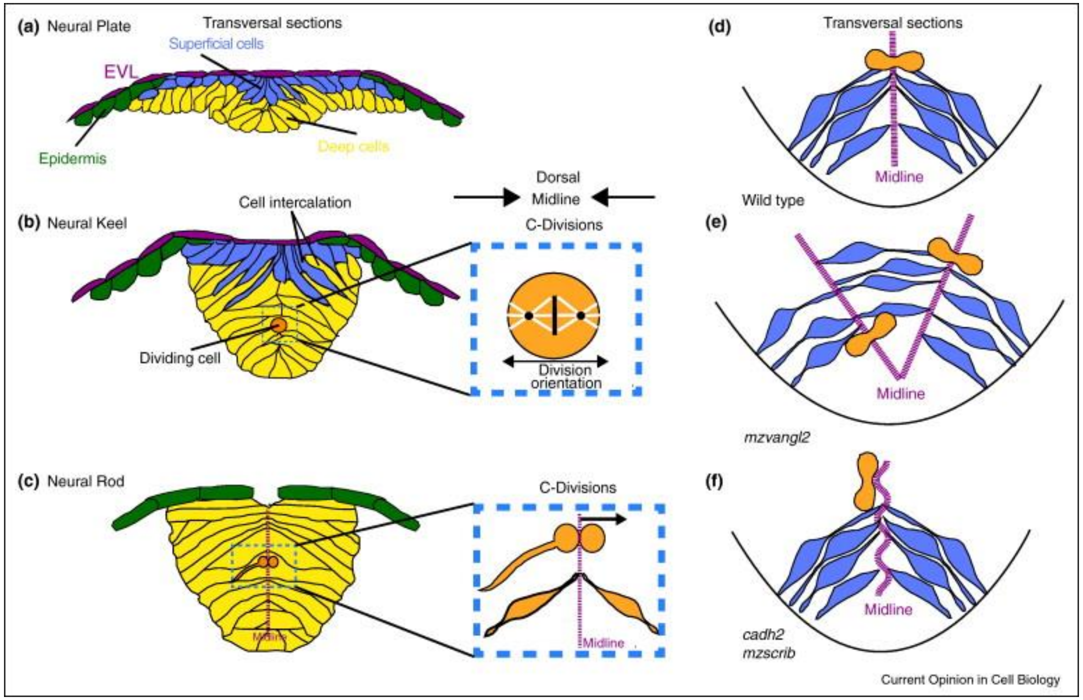
Planar cell polarity



Planar cell polarity

Regulation of cellular processes involved in tissue morphogenesis, migration and mechanosensing by apical/basal polarity factors and PCP proteins

Oriented cell division



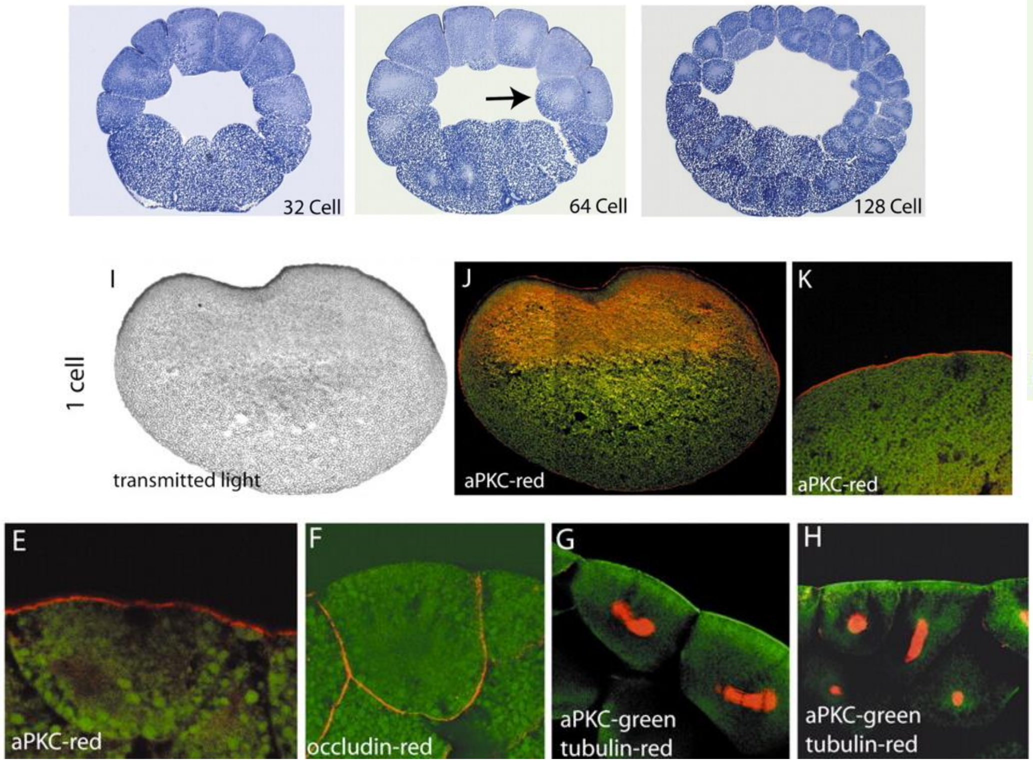
I Castanon, M González-Gaitán

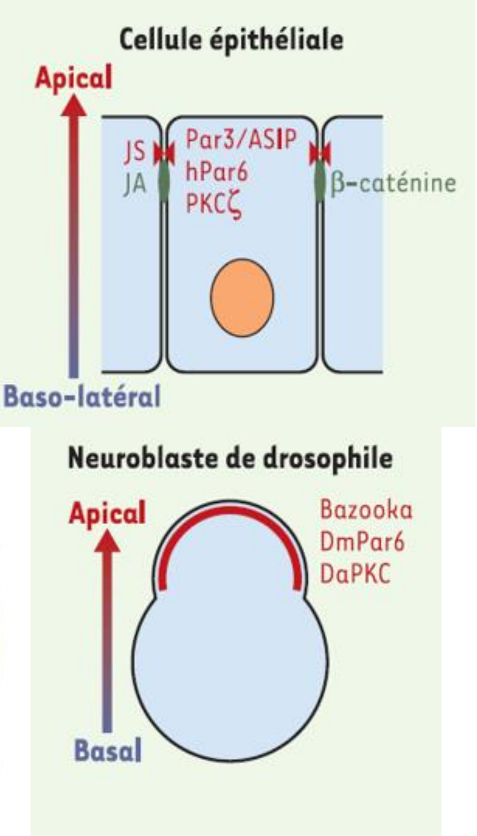
Oriented cell division in vertebrate embryogenesis

Current Opinion in Cell Biology, Volume 23, Issue 6, 2011, 697–704

Oriented cell division during zebrafish neurulation. (a–c) Major steps of neurulation in zebrafish embryos. (a) Neural plate. (b) Neural keel. Inset represents the orientation of cell divisions of neural progenitors at neural keel. The white lines represent microtubules. The black central line corresponds to condensated chromosomes and the black dots correspond to centrosomes. (c) Neural rod. Inset represents the cross divisions (Cdivisions), in which one of the daughter cells cross the midline (arrow). (d and e) Defects in midline formation in different mutant backgrounds compared to wild type. (d) Wild type neural keel. Cells of the mirror-image epithelia are represented in blue, dividing cells in orange, and the midline in purple. In wild type embryos, cells divide close to the midline and one of the cells is integrated into the contralateral epithelium. (e) Neural keel in maternal-zygotic vangl2 (mzvangl2) mutants. These embryos display ectopic midlines probably due to deficient dorsal convergence, while C-divisions are normal. (f) Neural keel in cadh2 and mzscrib mutants. These embryos showed abnormal midline morphology. C-divisions are impaired.

Vertebrate embryos are characterized by a MULTILAYERED organization
Separation of outer and inner cells in the early Xenopus embryo



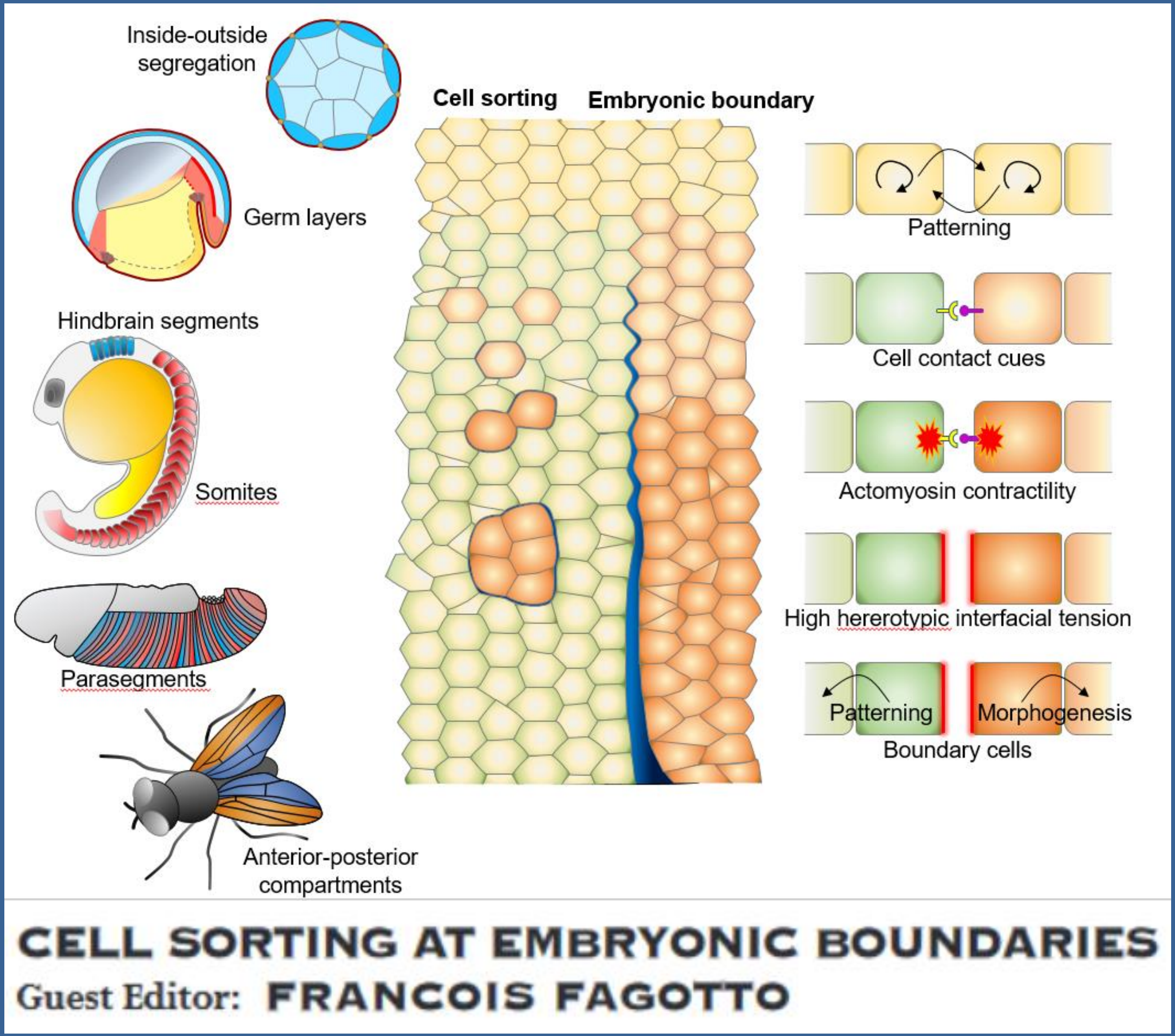


BioCell M1

aPKC is apically localised and asymmetrically inherited during the perpendicular divisions.

Andrew D. Chalmers et al. Development 2003;130:2657-2668
See for review: Fagotto. Seminars in Cell Developmental Biology 2020; 107, 130-146

Development

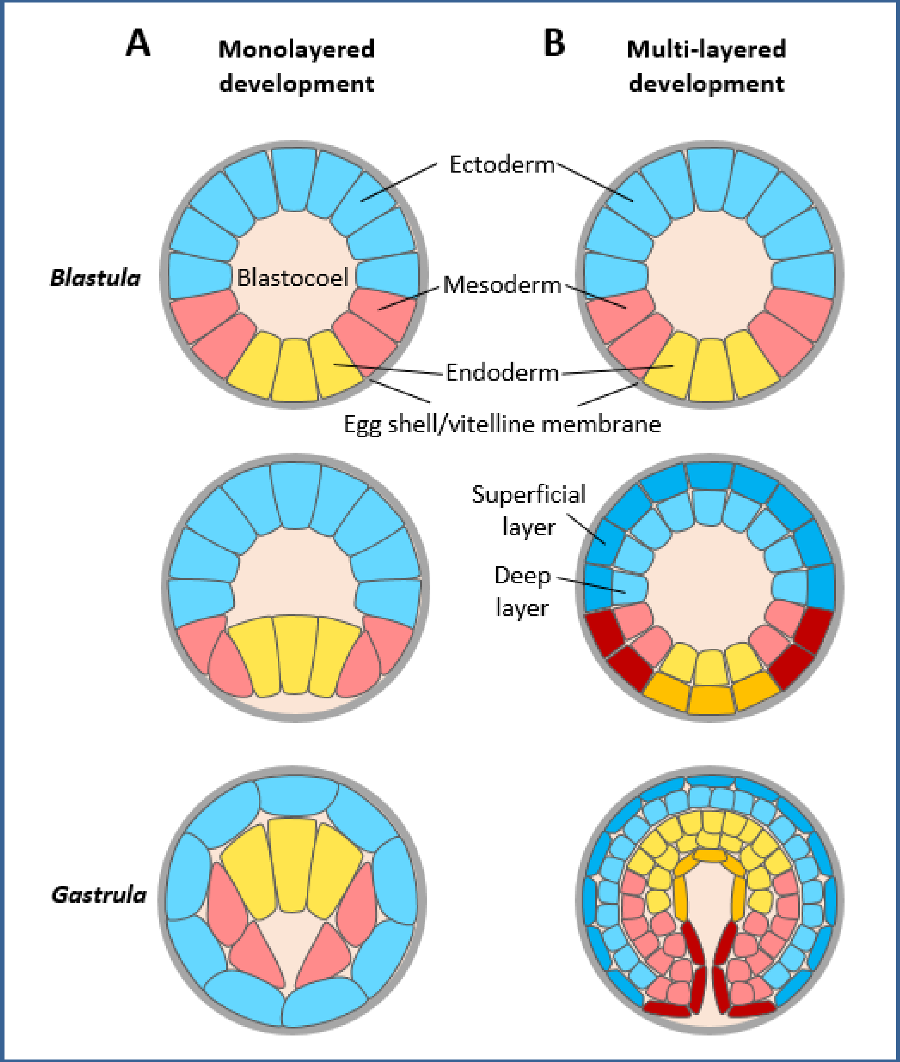


CELL SORTING AT EMBRYONIC BOUNDARIES

Guest Editor: **FRANCOIS FAGOTTO**

SEMIN. CELL DEV. BIOL. *107* (2020), 126-129

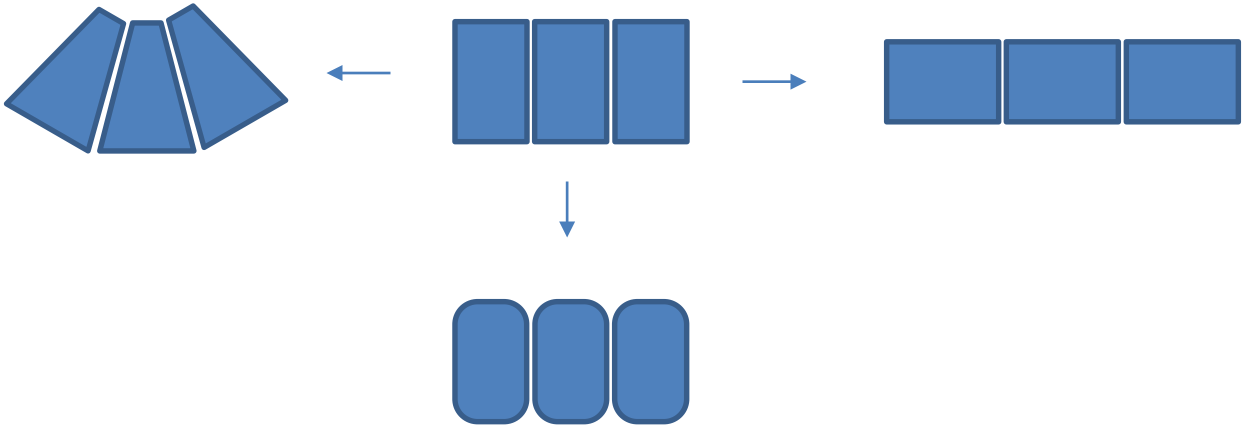
Tissue segregation in the early vertebrate embryo



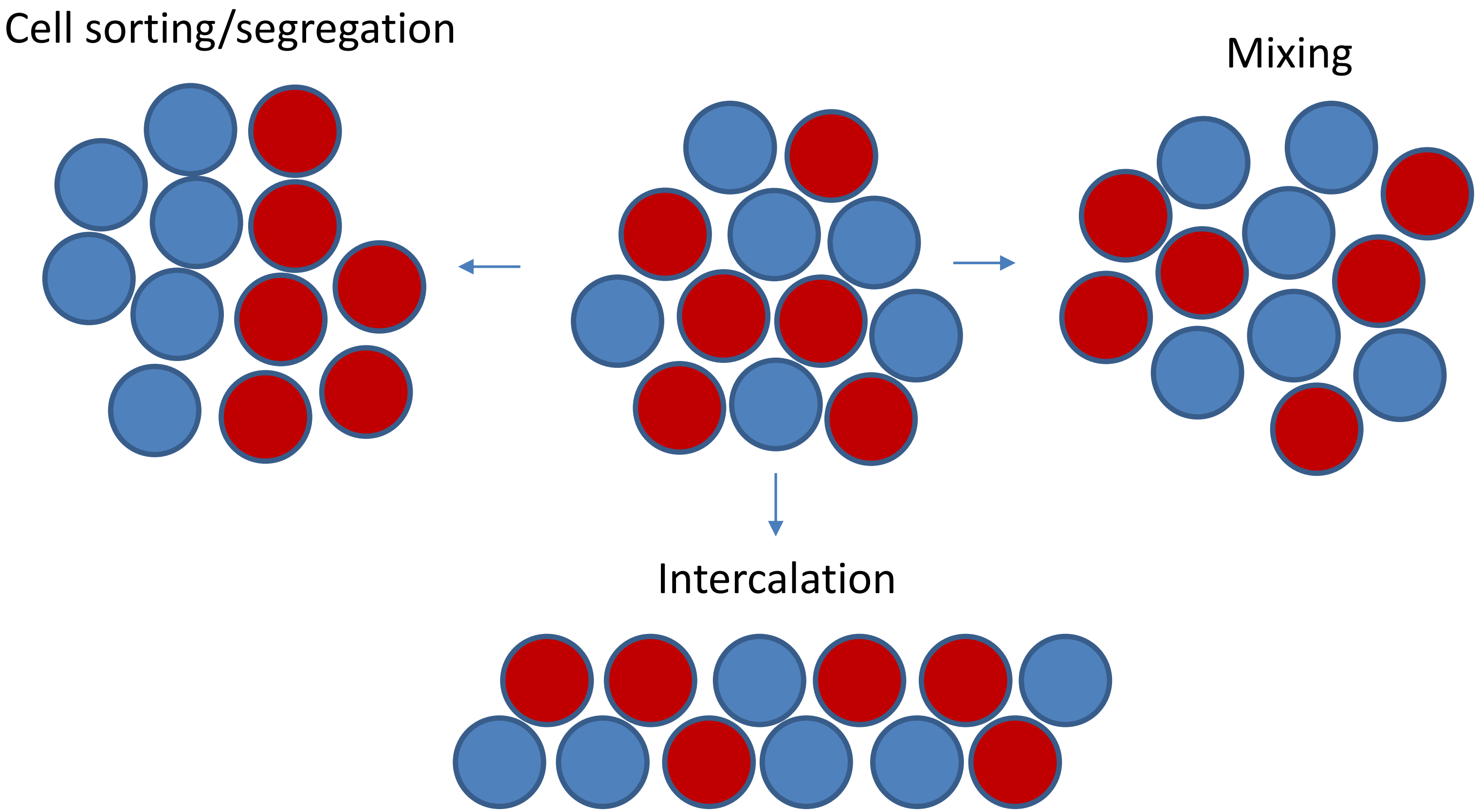
Fagotto, F. Semin. Cell Dev. Biol. *107* (2020), 130-146

Cell shape, motility and rearrangement

Changes in cell shape



Changes in cell positioning

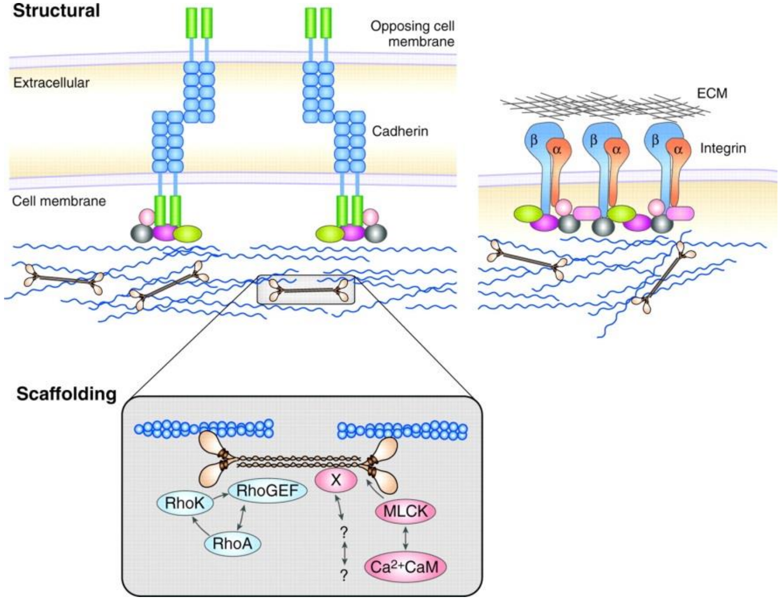


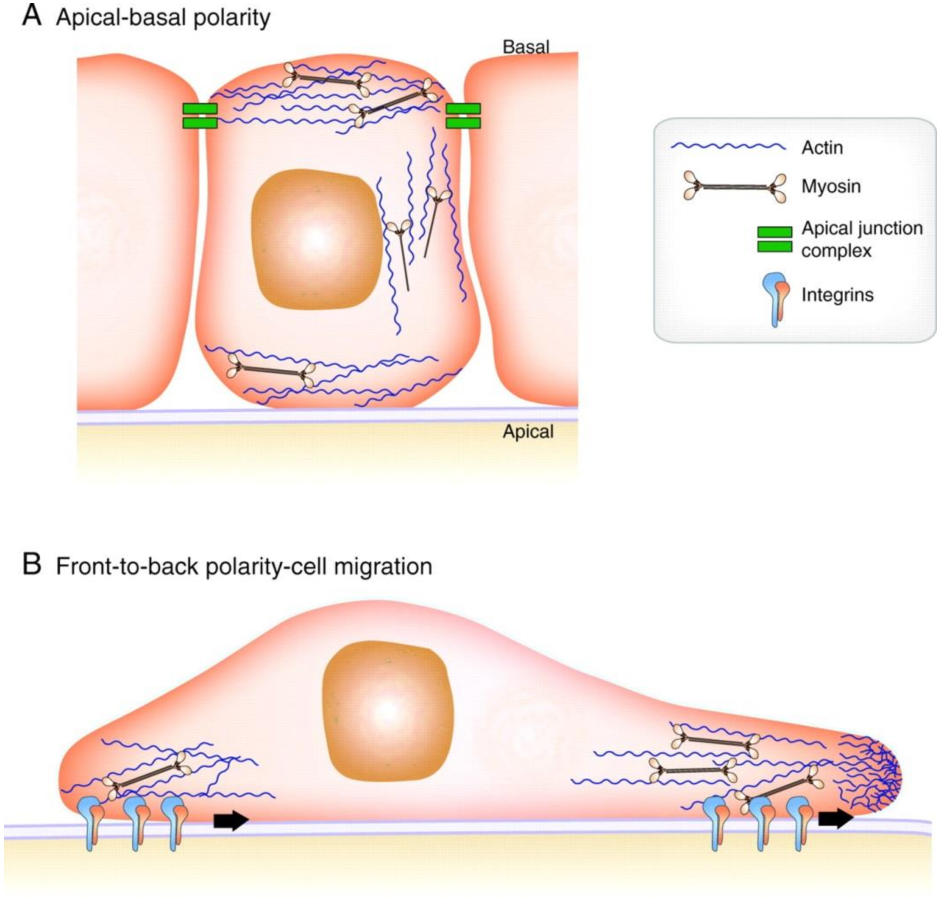
Cell sorting/segregation

Mixing

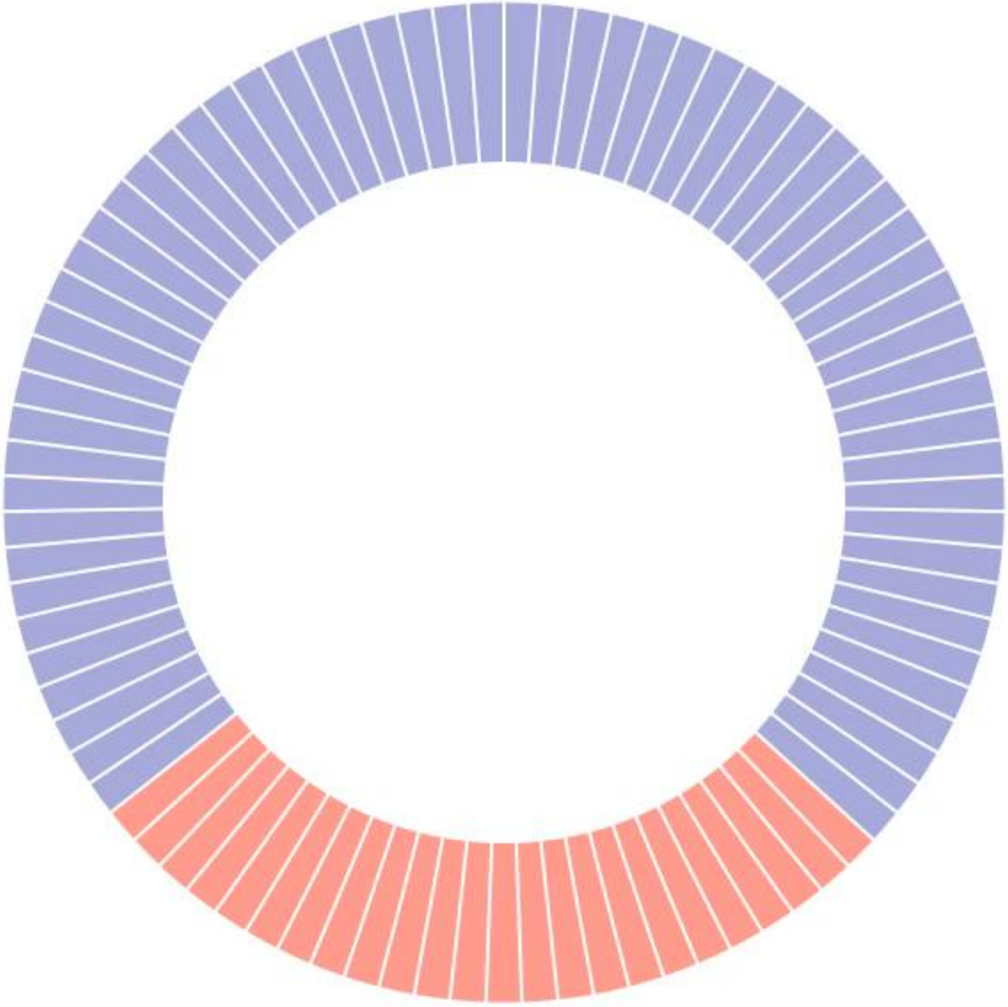
Intercalation

Morphogenesis at the cellular level: Importance of the contractile actomyosin cytoskeleton

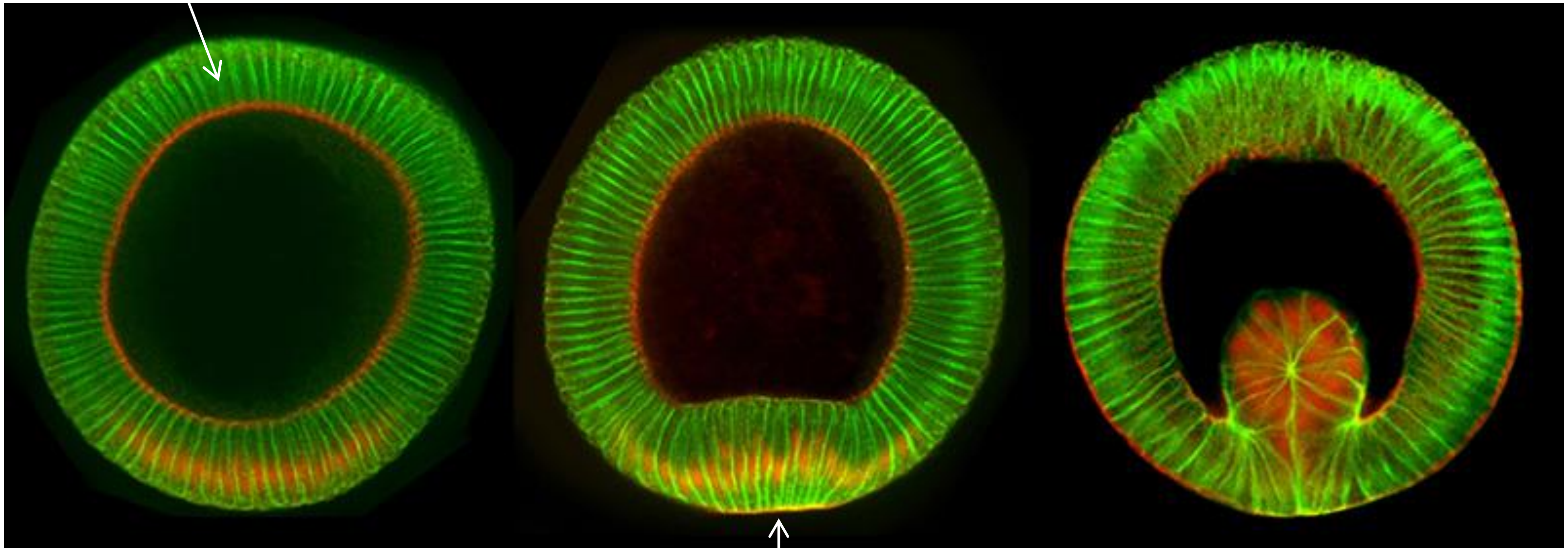




Changes in cell shape: Gastrulation by invagination: Simulation of endoderm invagination in cnidarians



Changes in cell shape: Drosophila gastrulation

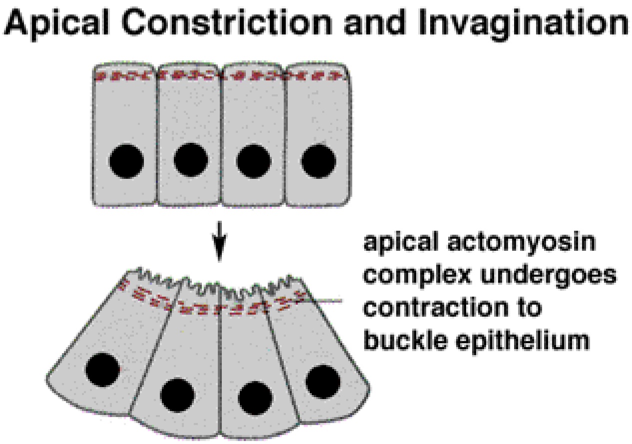


Blastoderm

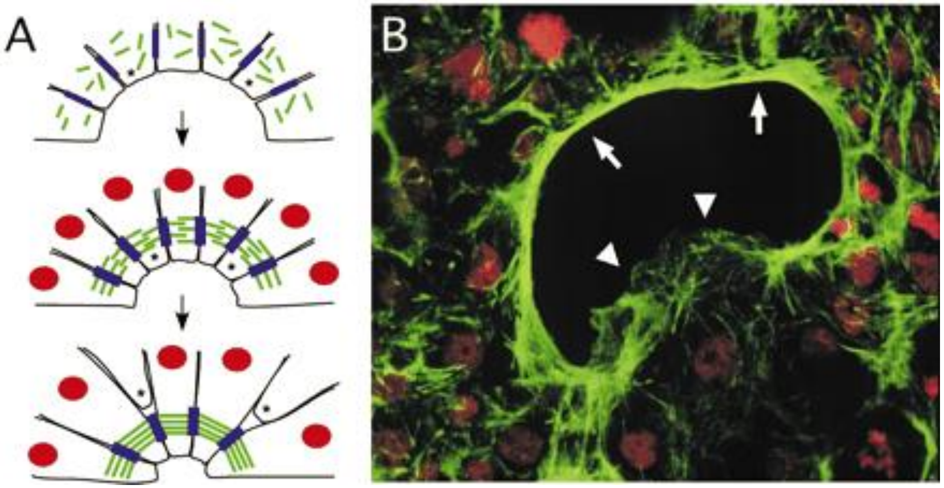
Dorsal

Ventral fullow

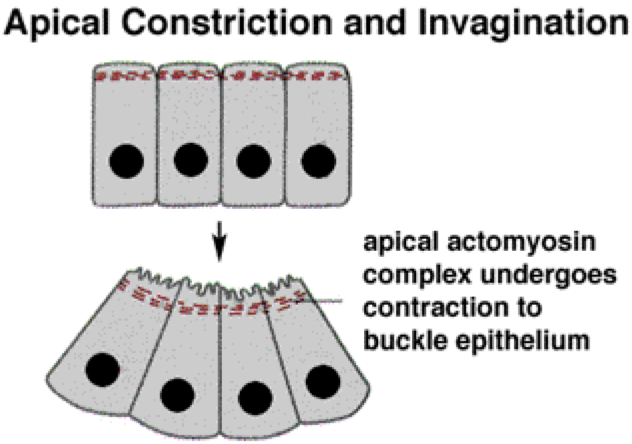
Morphogenesis at the cellular level:
Importance of the contractile actomyosin cytoskeleton



Invagination: Parallel with epithelial wound healing, uses the same machinery

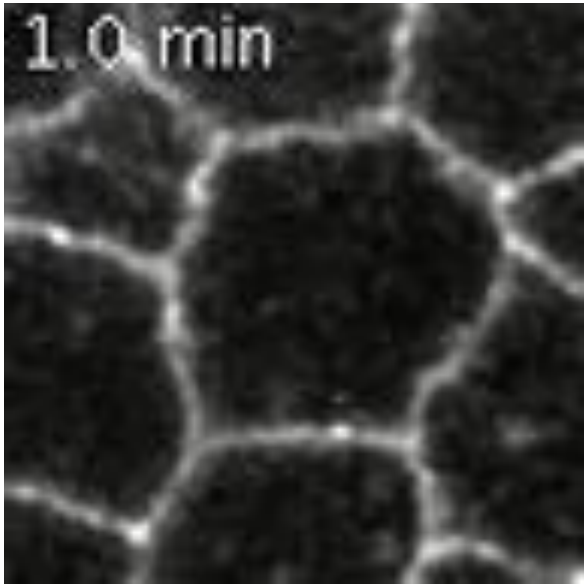


Morphogenesis at the cellular level: Importance of the contractile actomyosin cytoskeleton



?

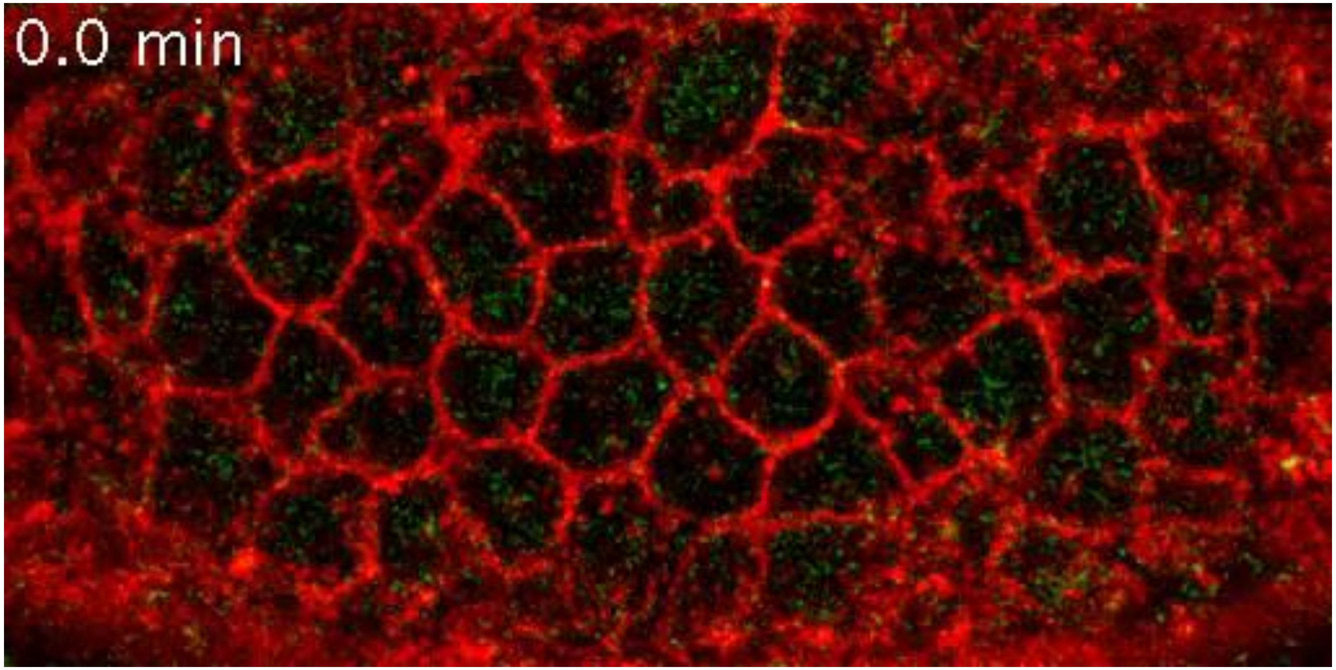
Actin contraction during Drosophila gastrulation

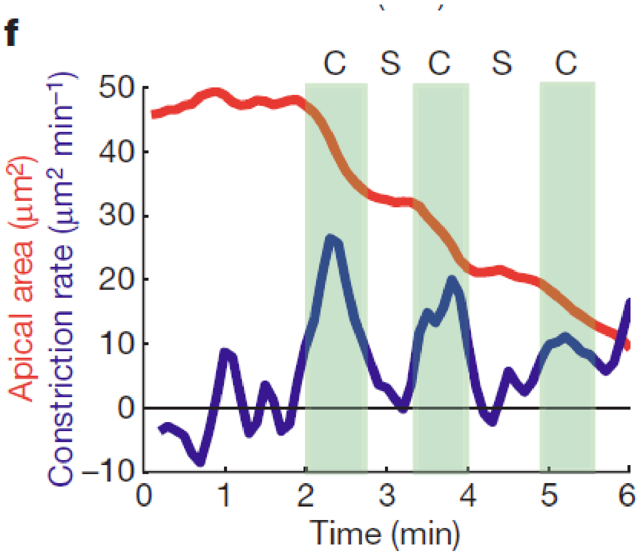


Bursts of myosin contraction during Drosophila gastrulation

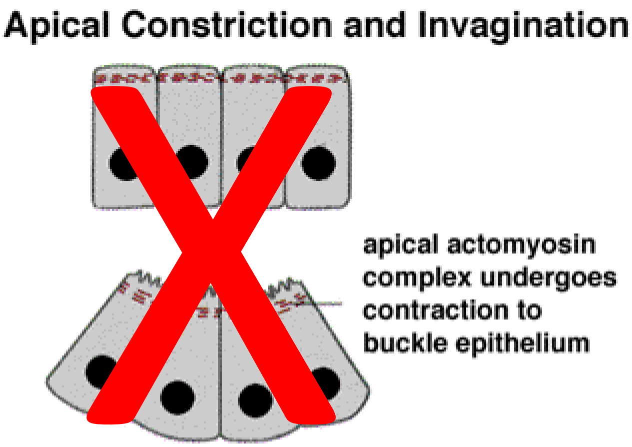
Cadherin

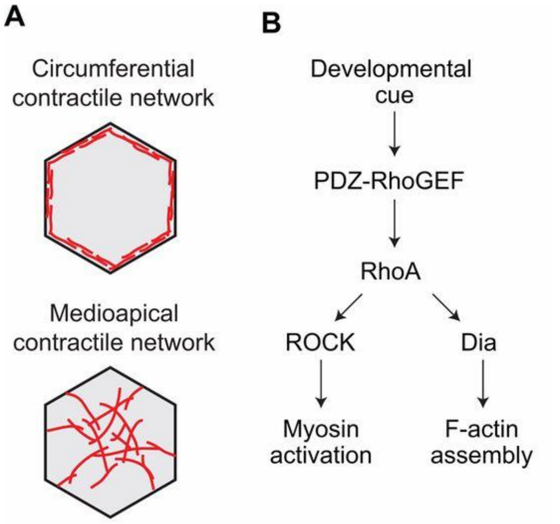
Myosin



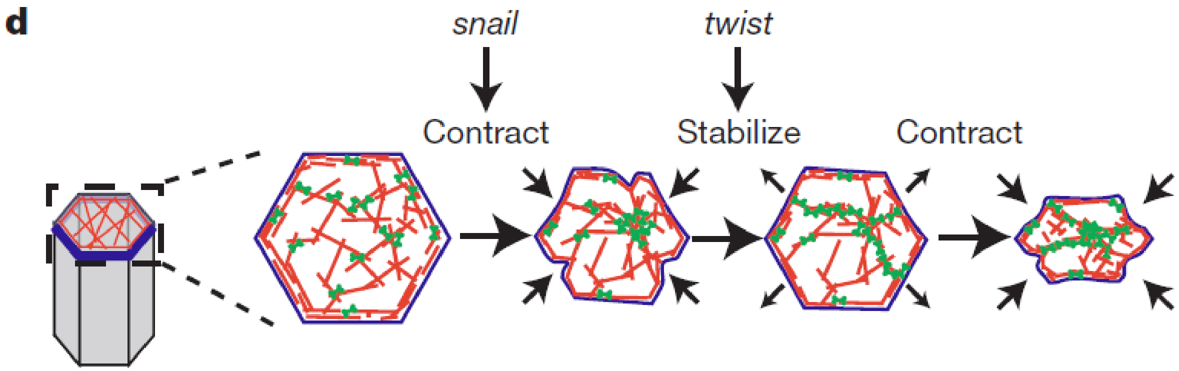


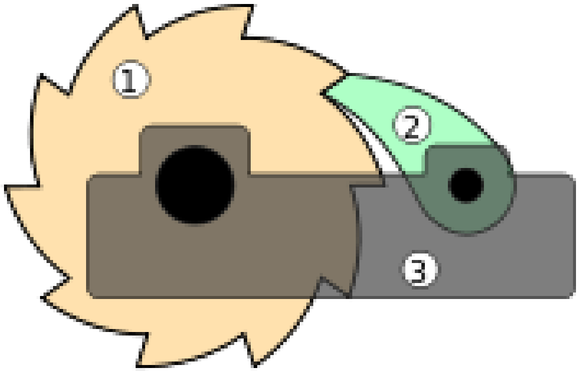
Morphogenesis at the cellular level:
Importance of the contractile actomyosin cytoskeleton



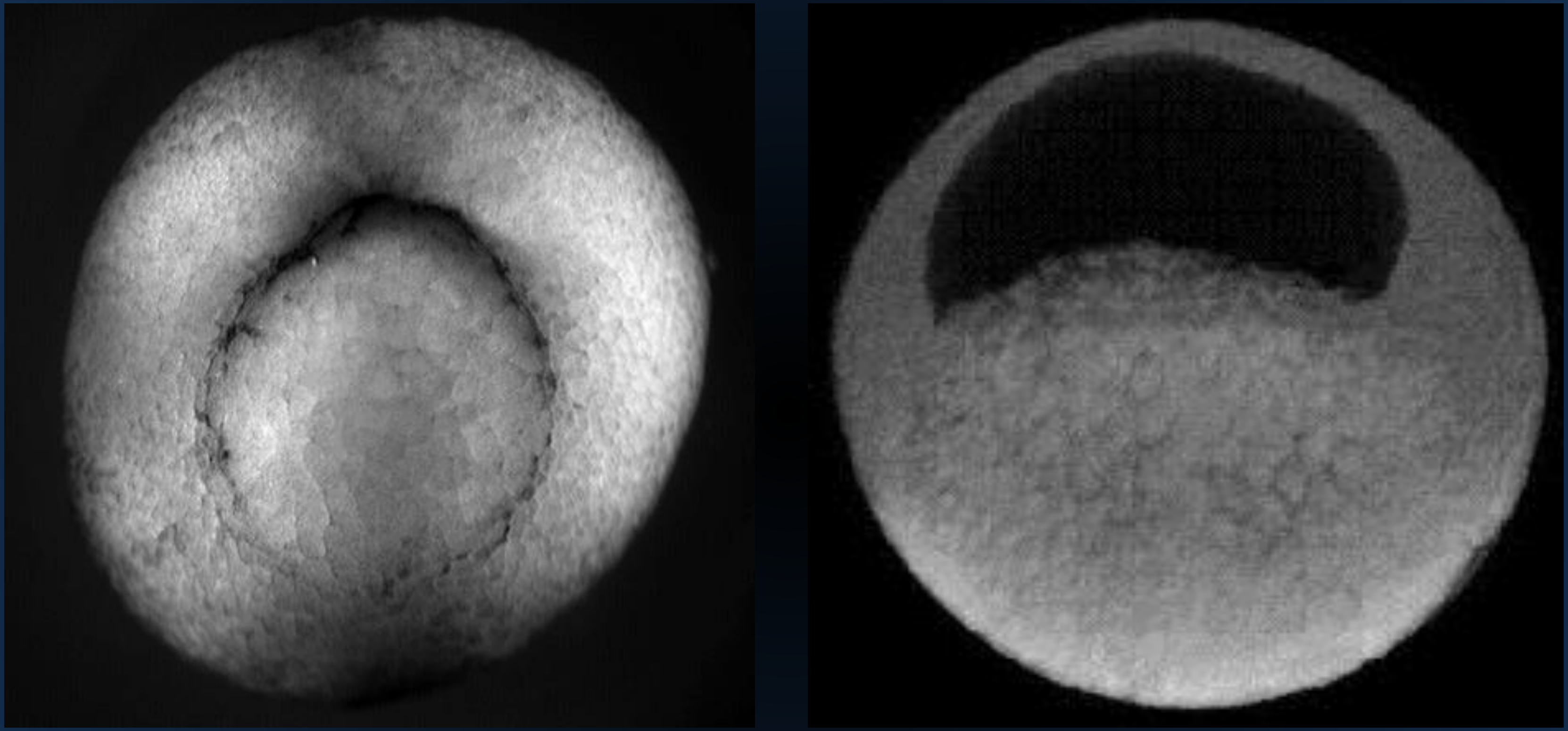


Ratchet mechanism of apical constriction

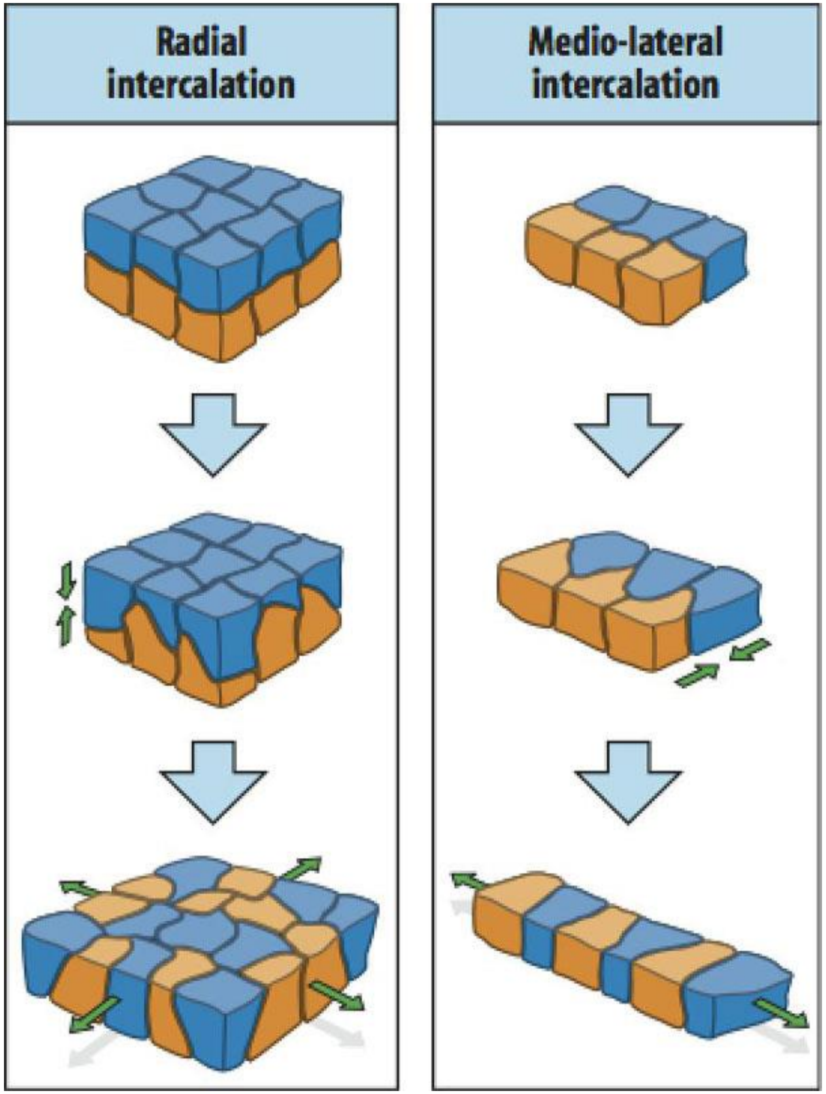




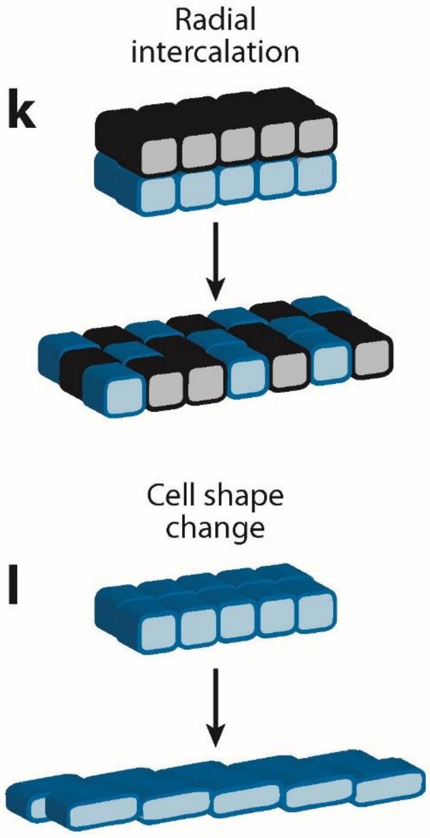
Xenopus gastrulation



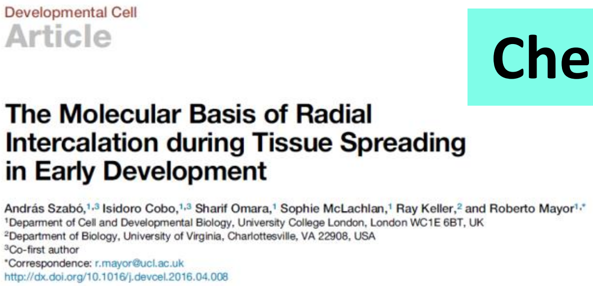
Basic cell rearrangements during morphogenesis



Ectoderm epiboly



Chemotaxis orients intercalation

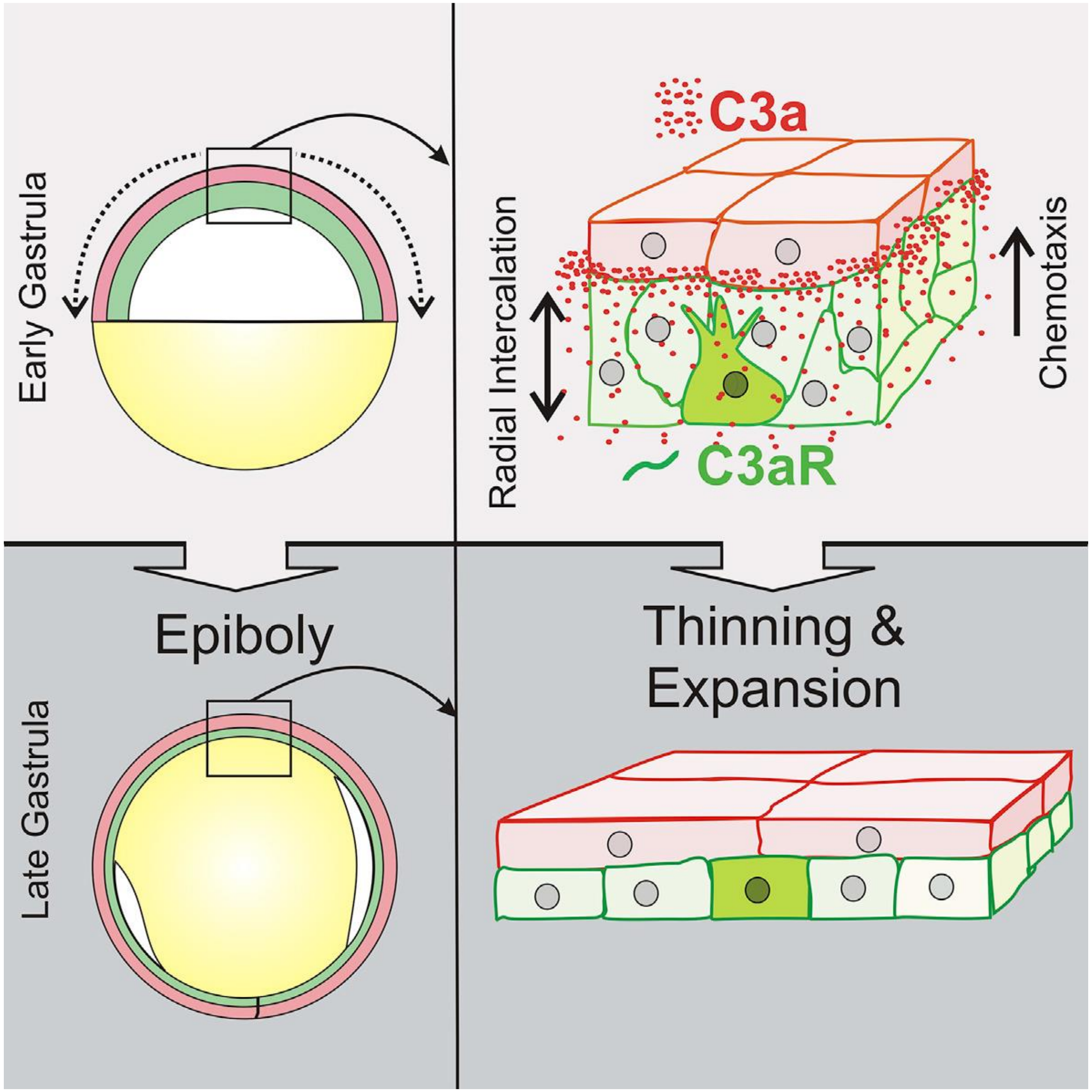


Developmental Cell
Article

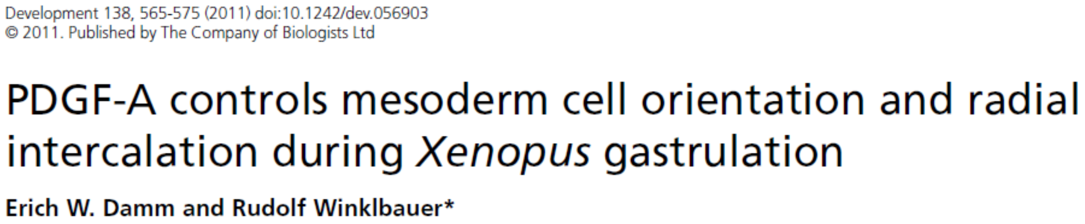
The Molecular Basis of Radial Intercalation during Tissue Spreading in Early Development

András Szabó,[1,3] Isidoro Cobo,[1,3] Sharif Omara,[1] Sophie McLachlan,[1] Ray Keller,[2] and Roberto Mayor[1,*]
[1]Deparment of Cell and Developmental Biology, University College London, London WC1E 6BT, UK
[2]Department of Biology, University of Virginia, Charlottesville, VA 22908, USA
[3]Co-first author
*Correspondence: r.mayor@ucl.ac.uk
http://dx.doi.org/10.1016/j.devcel.2016.04.008

Ectoderm epiboly



Chemotaxis orients intercalation

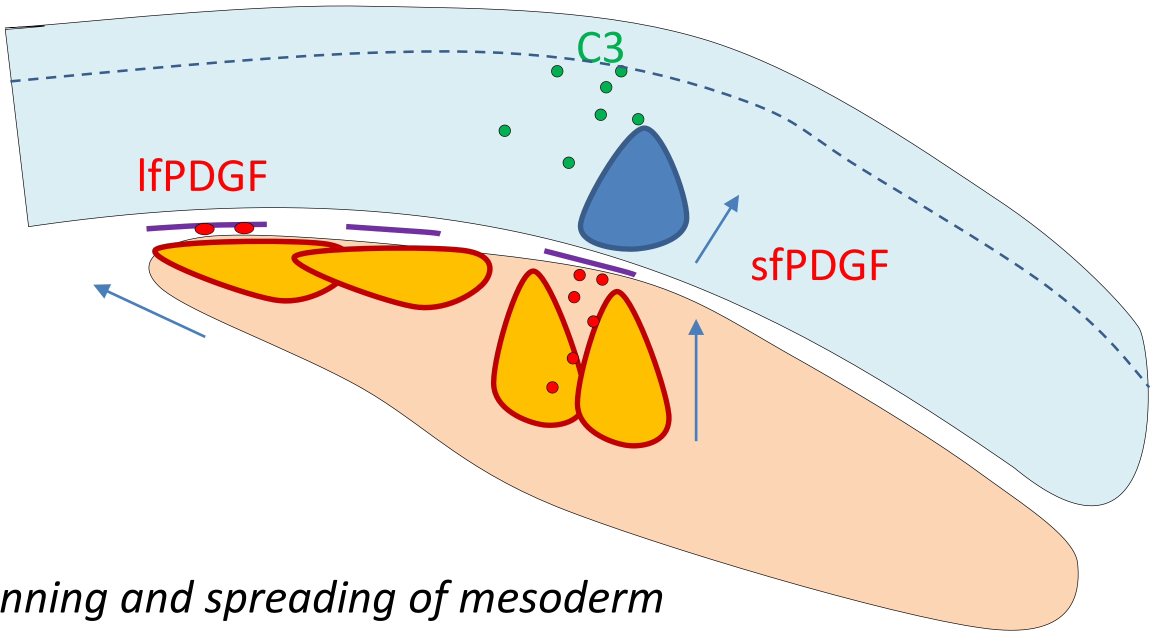


Development 138, 565-575 (2011) doi:10.1242/dev.056903

PDF-A controls mesoderm cell orientation and radial intercalation during *Xenopus* gastrulation

Erich W. Damm and Rudolf Winklbauer*

Thinning and spreading of ectoderm

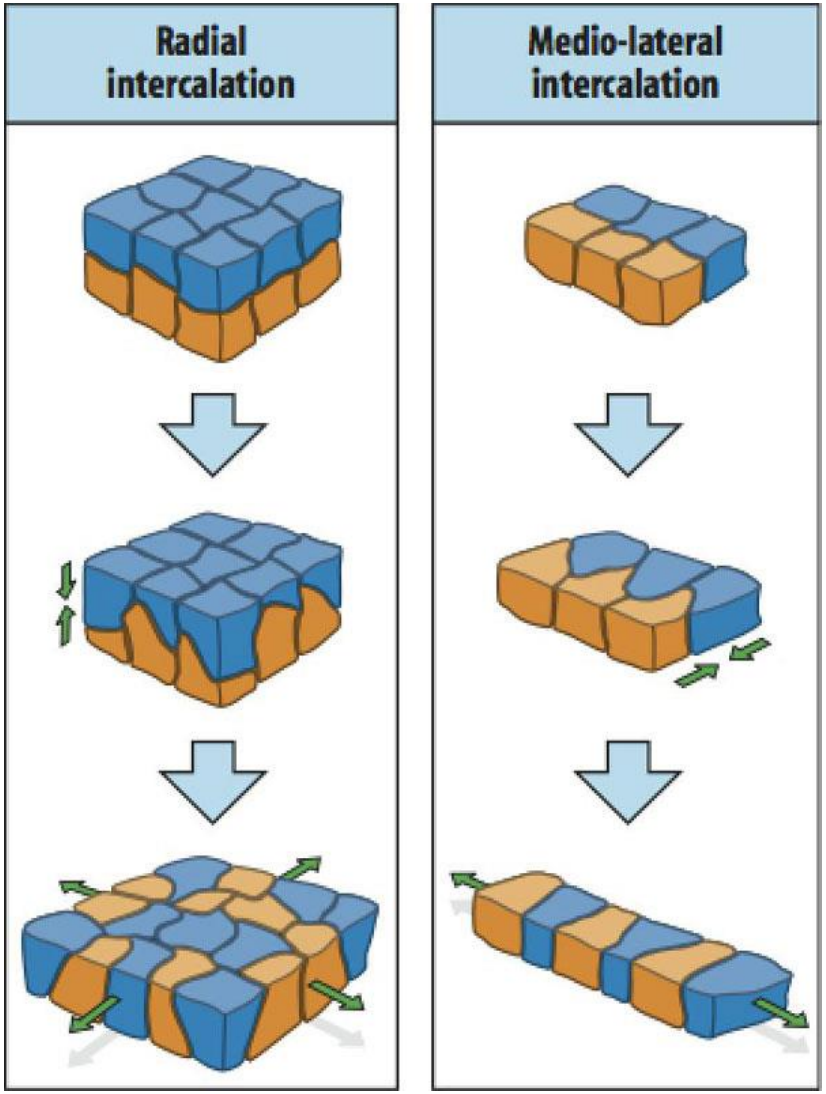


Thinning and spreading of mesoderm

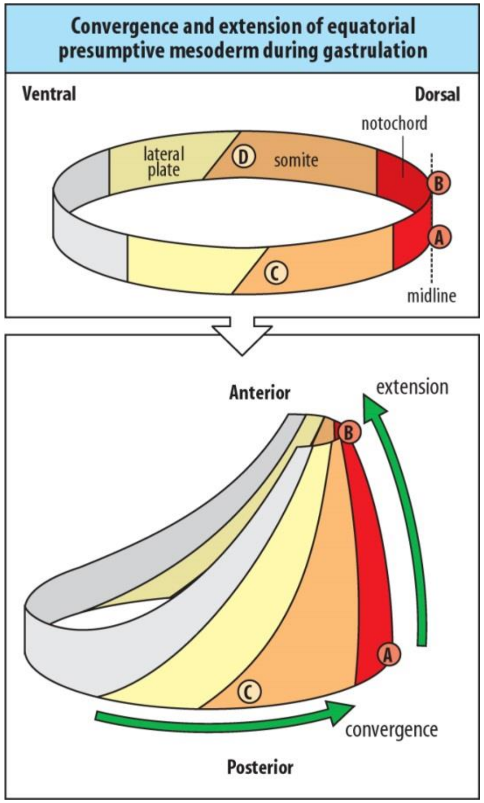
Convergent extension

Tissue elongation:
medio-lateral intercalation = convergent extension

Ray Keller

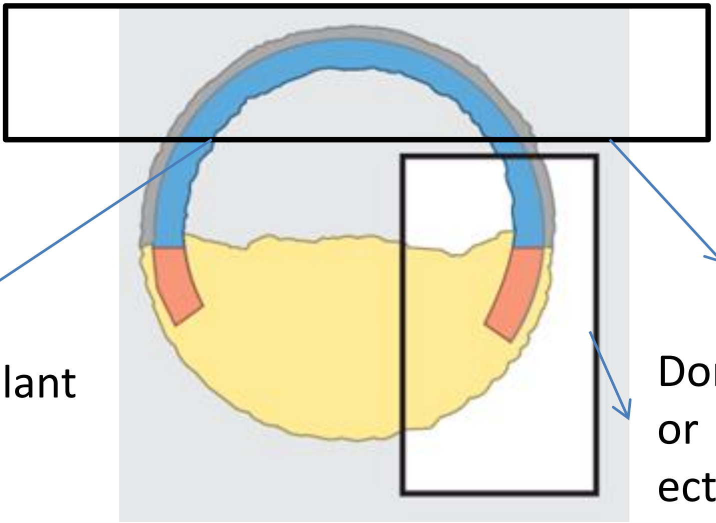


Tissue elongation:
medio-lateral intercalation = convergent extension



Convergence and extension of equatorial presumptive mesoderm during gastrulation

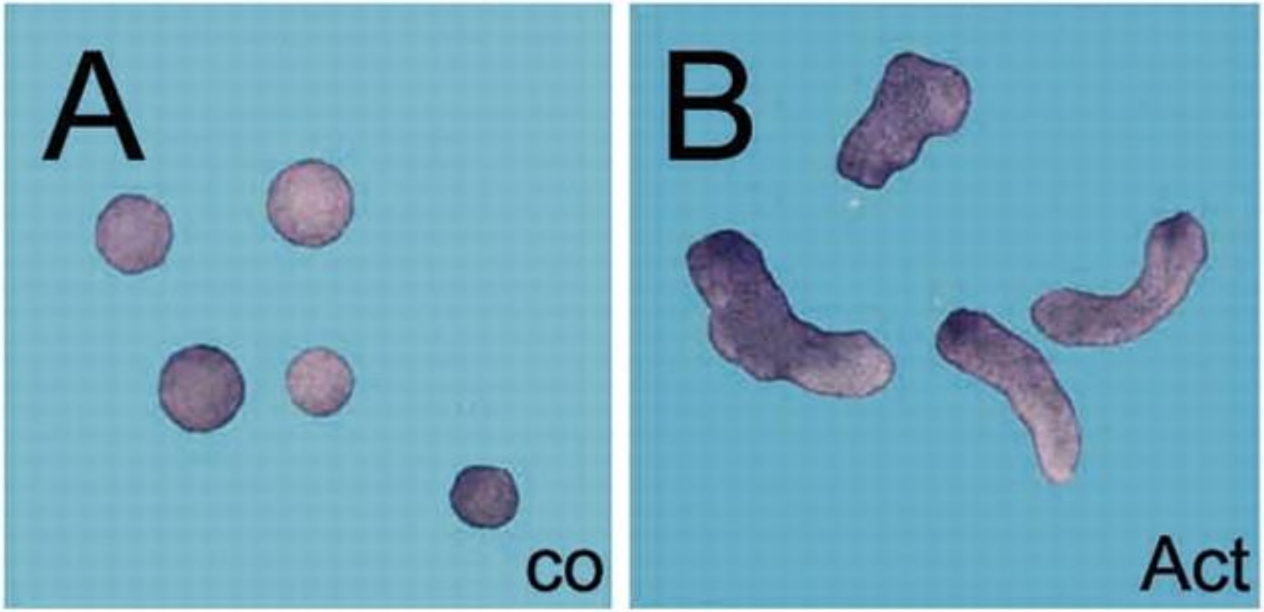
Tissue elongation: autonomy and induction by TGFβ signaling



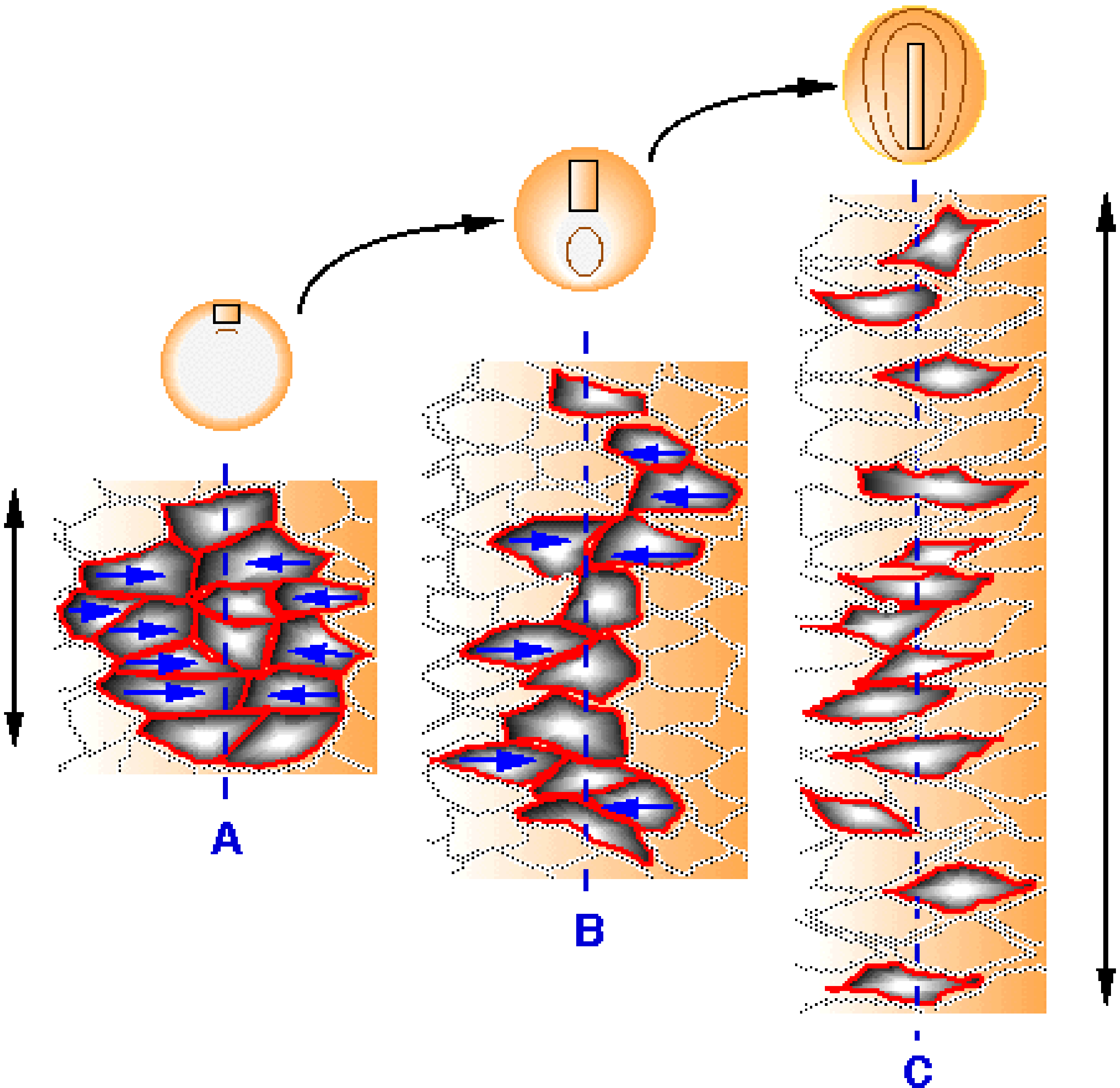
Ectoderm explant

+activin

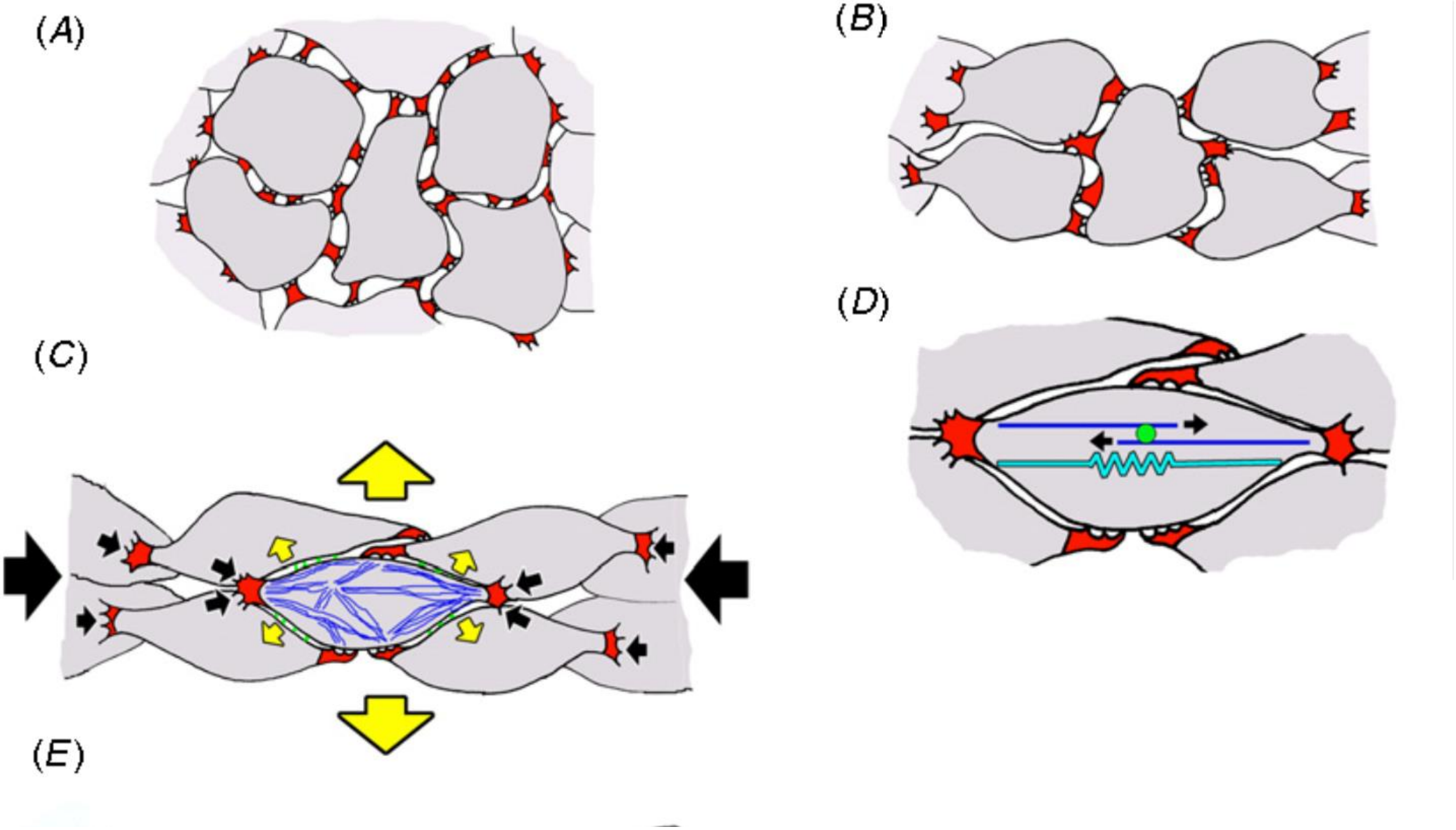
Dorsal mesoderm explant
or
ectoderm explant treated
with activin/Nodal (TGFβ)



Tissue elongation: Neural tube

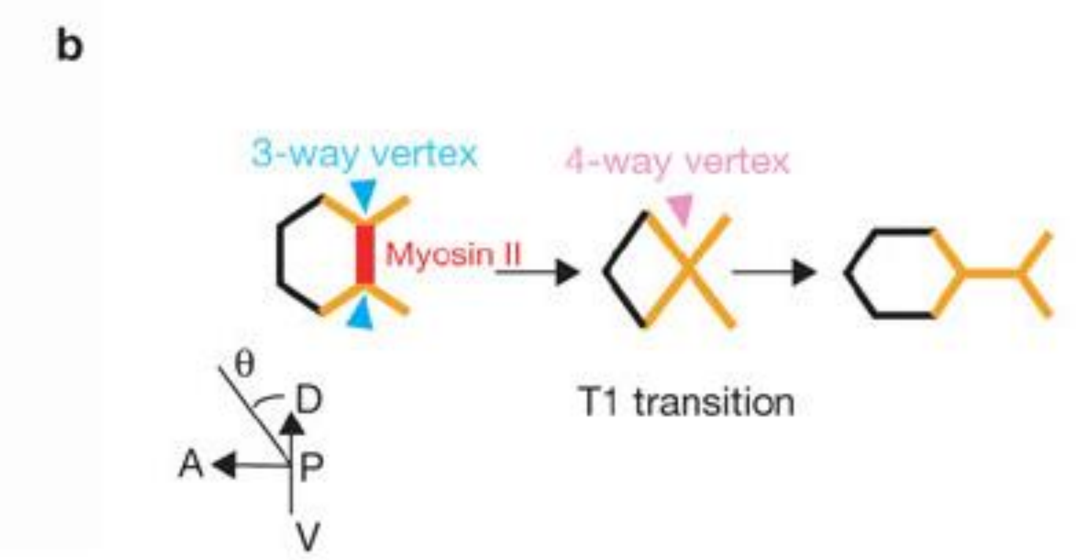


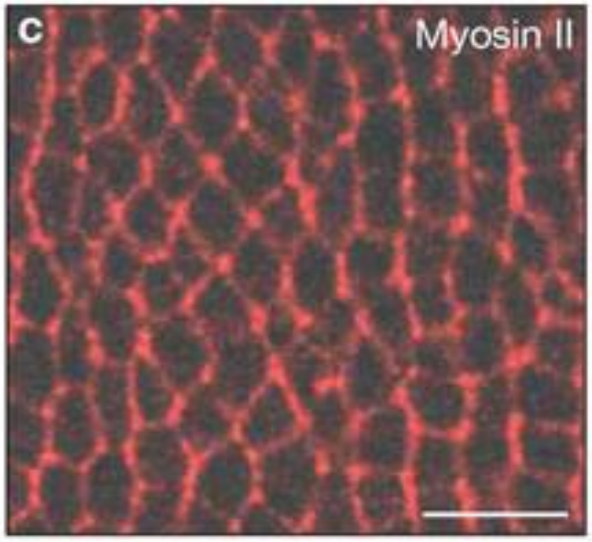
Convergent extension: polarization of protrusions

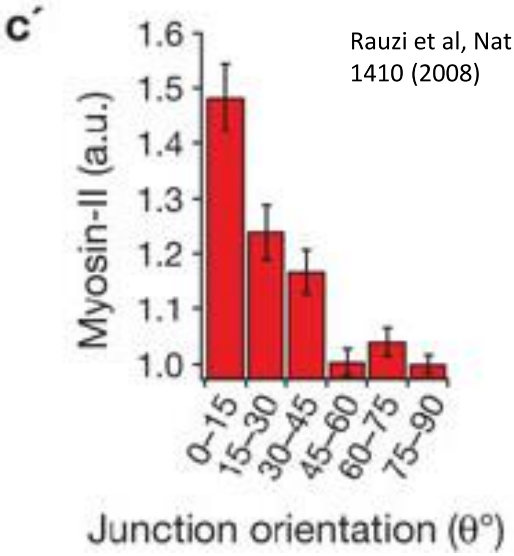


Convergent extension: polarization of contractile actomyosin cytoskeleton

Lecuit and Zallen labs

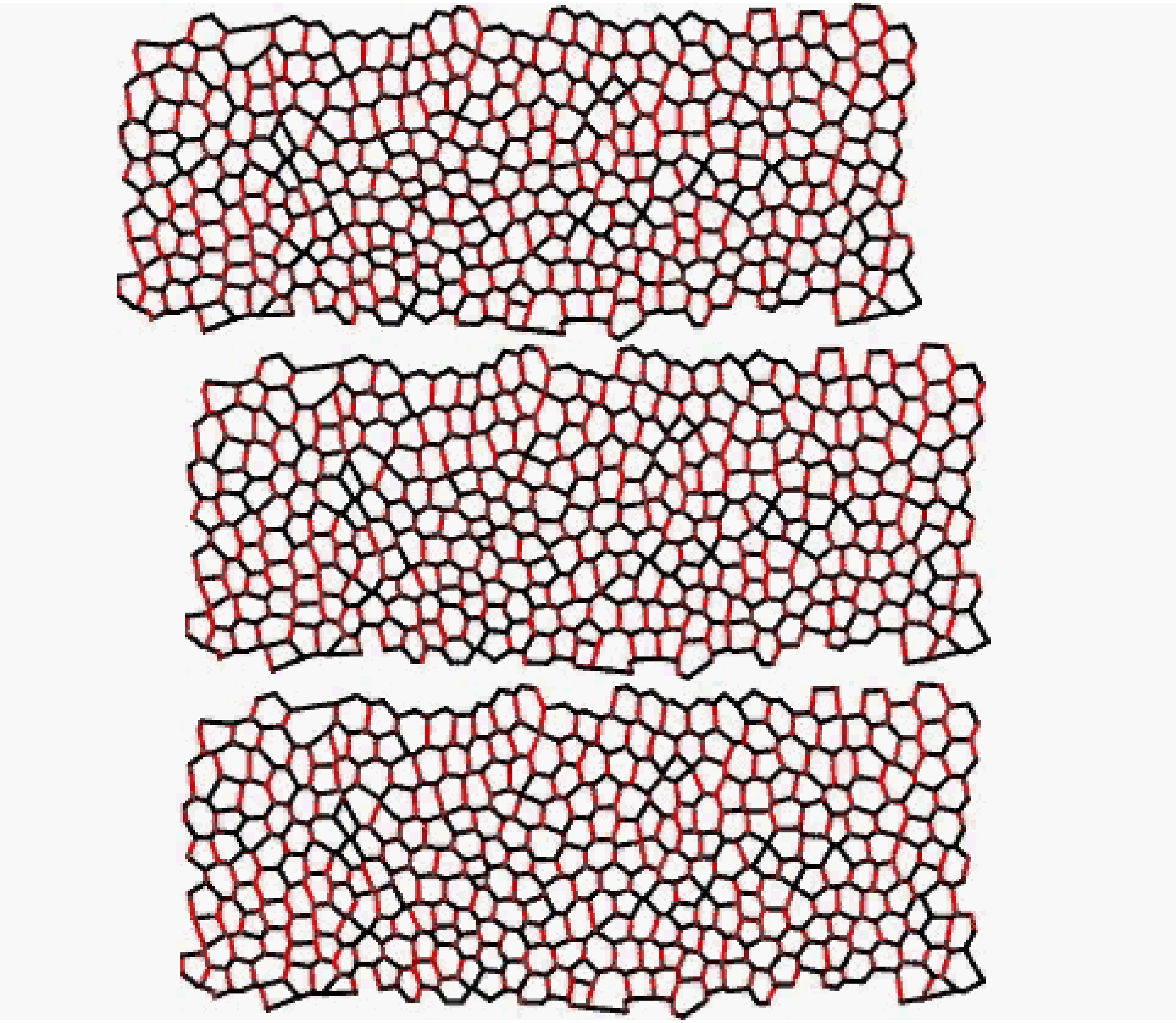




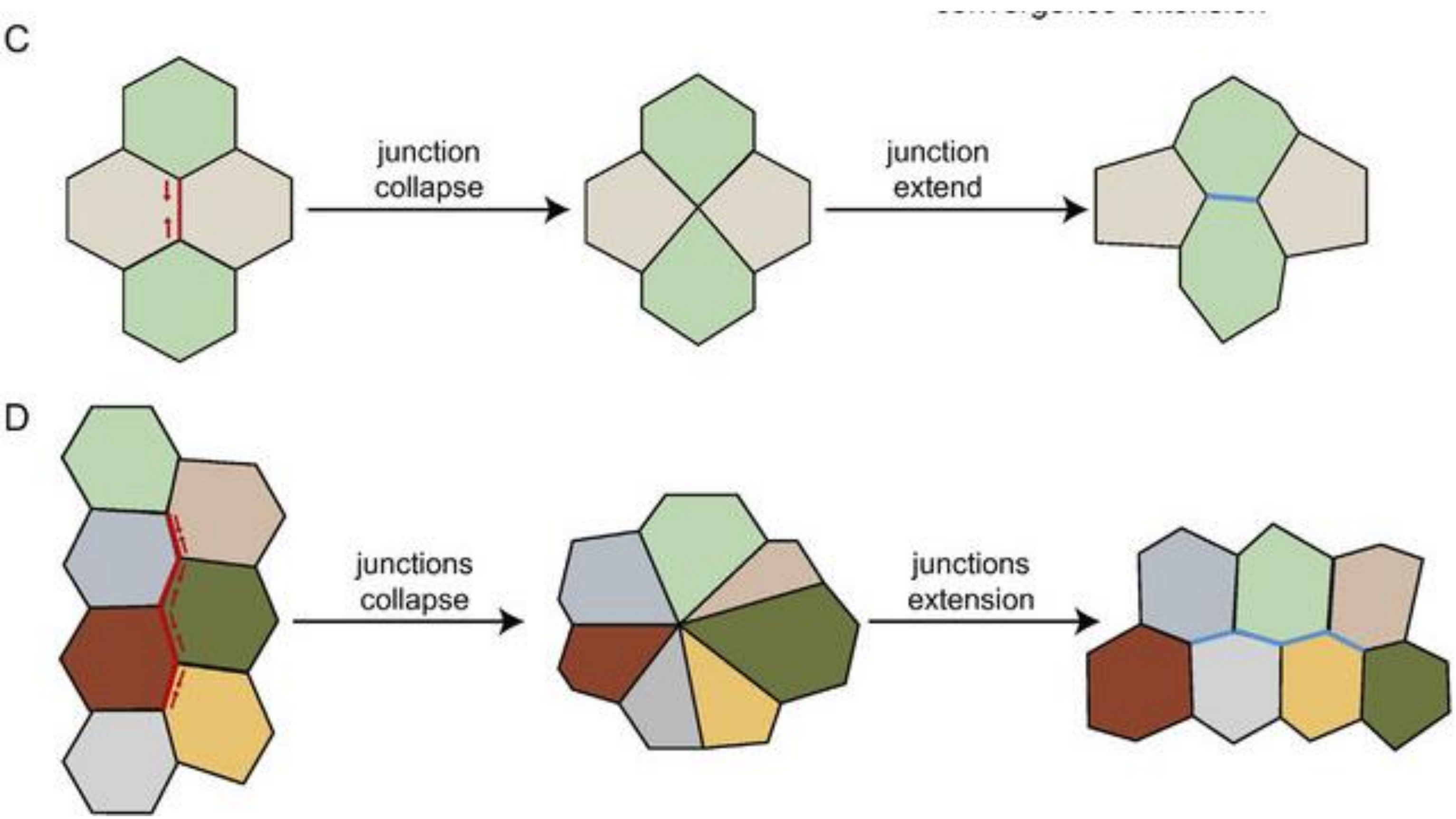


Rauzi et al, Nature Cell Biology 10, 1401 - 1410 (2008)

Convergent extension: polarization of contractile actomyosin cytoskeleton

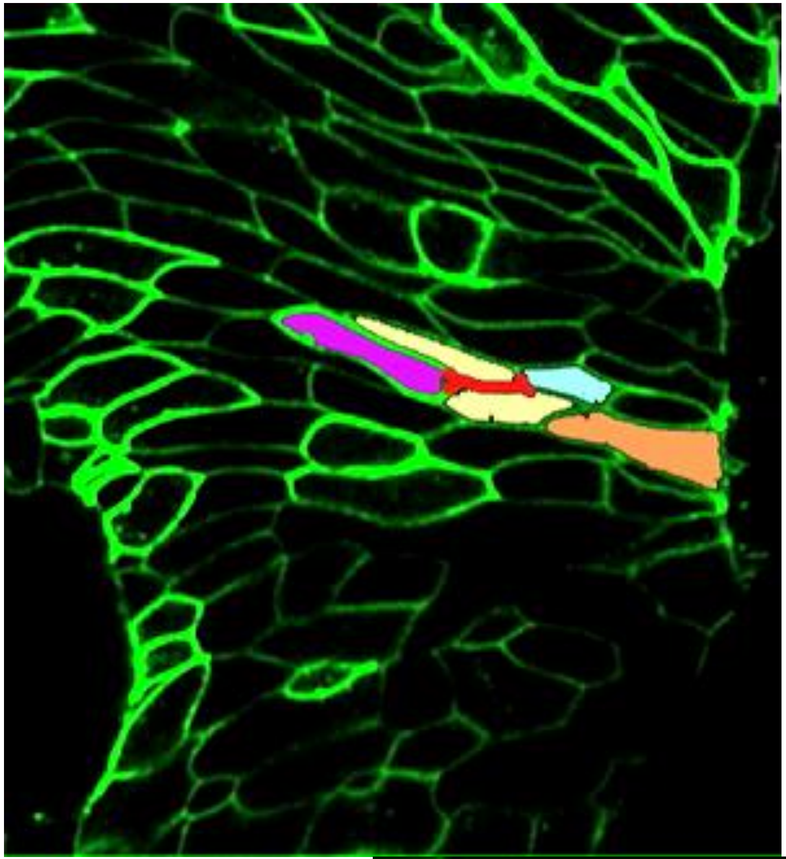


Convergent extension: polarization of contractile actomyosin cytoskeleton

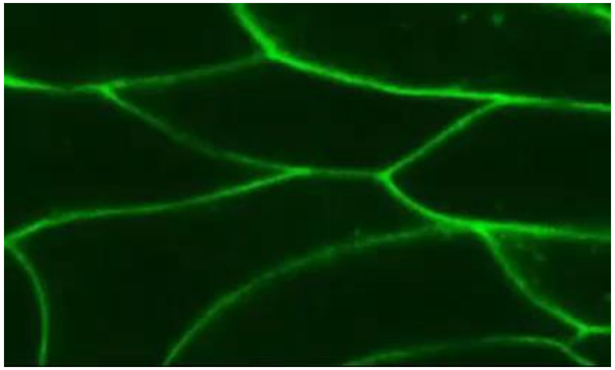


Forces directing germ-band extension in Drosophila embryos
- April 2017
- Mechanisms of Development 144(Pt A):Pages 11-22

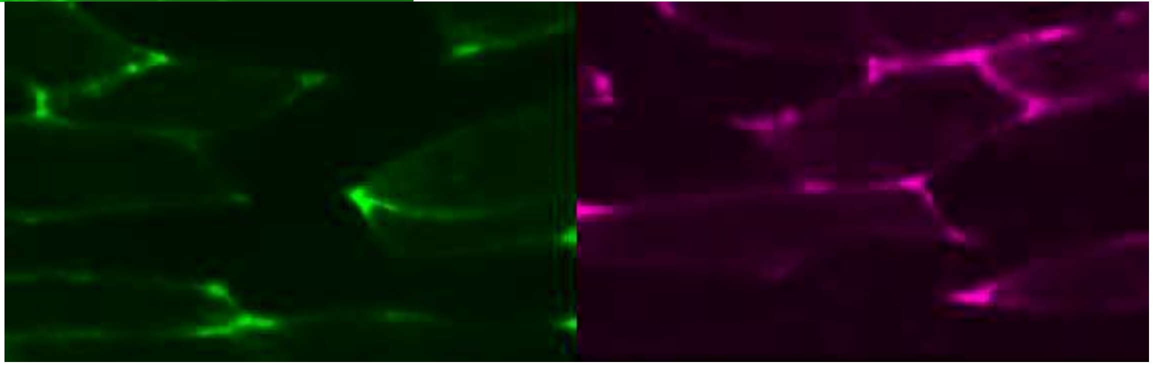
Convergence-extension in Xenopus



Laser ablation



Actin

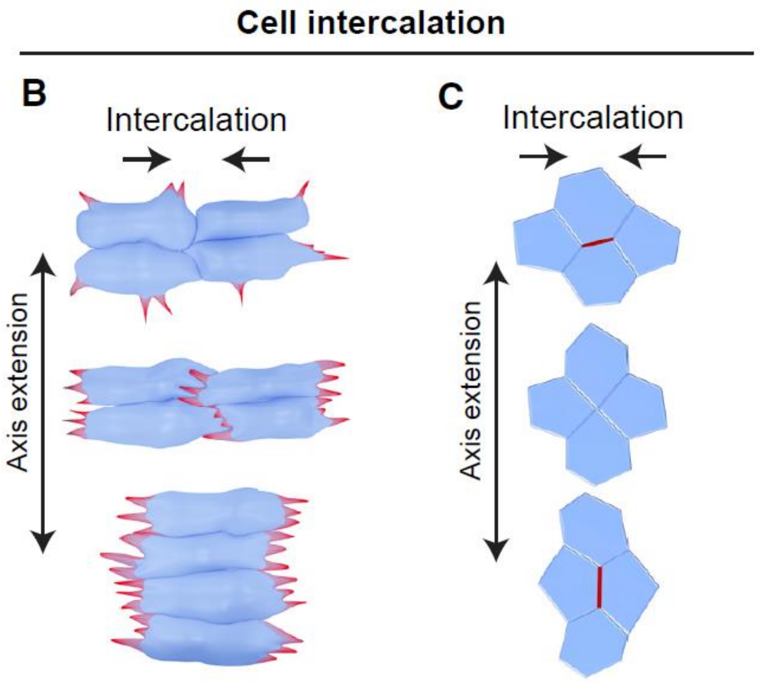


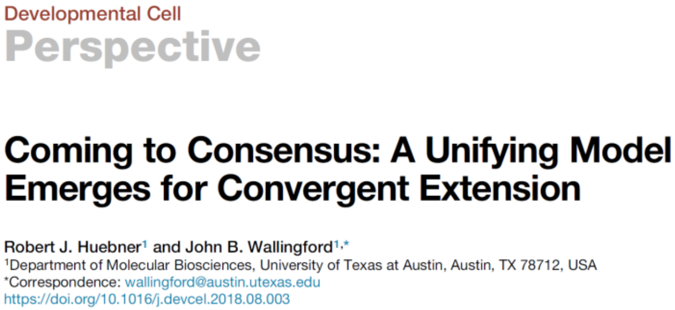
John Wallingford team
Shindo and Wallingford

Convergent extension: polarization of contractile actomyosin cytoskeleton versus protrusive crawling

Basolateral protrusion and apical contraction cooperatively drive *Drosophila* germ-band extension

Zijun Sun[1], Christopher Amourda[1], Murat Shagirov[1], Yusuke Hara[1], Timothy E. Saunders[1,2,3] and Yusuke Toyama[1,2,4,5]





Developmental Cell

Perspective

Coming to Consensus: A Unifying Model Emerges for Convergent Extension

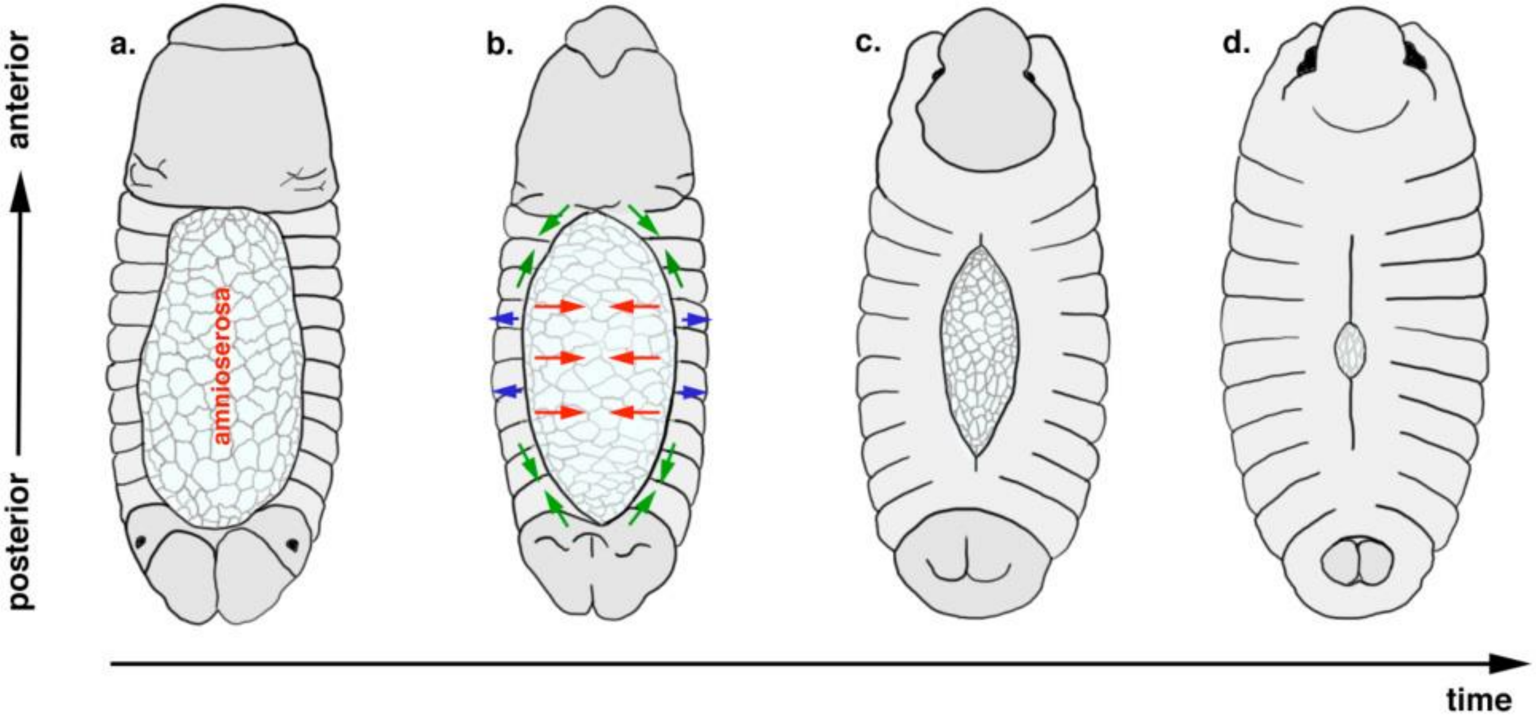
Robert J. Huebner[1] and John B. Wallingford[1,*]

[1]Department of Molecular Biosciences, University of Texas at Austin, Austin, TX 78712, USA

*Correspondence: wallingford@austin.utexas.edu

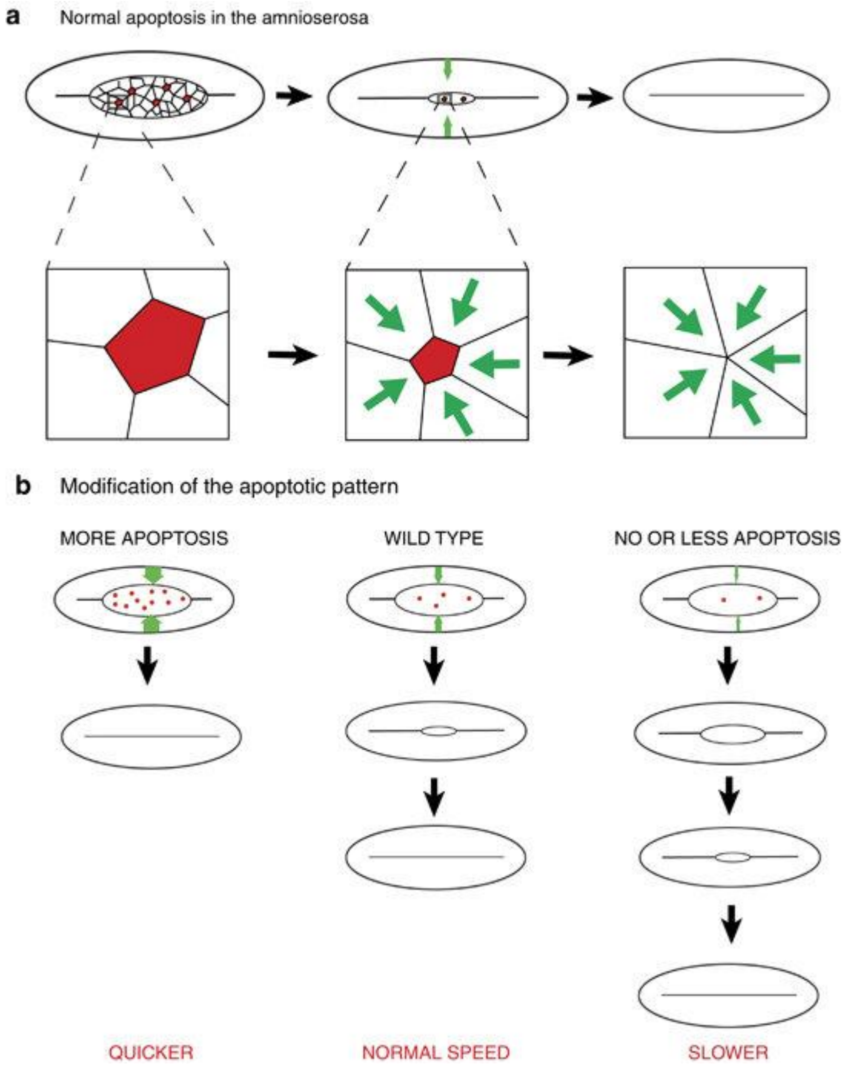
https://doi.org/10.1016/j.devcel.2018.08.003

Drosophila dorsal closure (~ “Wound healing”)



Dorsal closure
https://www.youtube.com/watch?v=rj95YkQSyic

Drosophila dorsal closure (~ “Wound healing”)

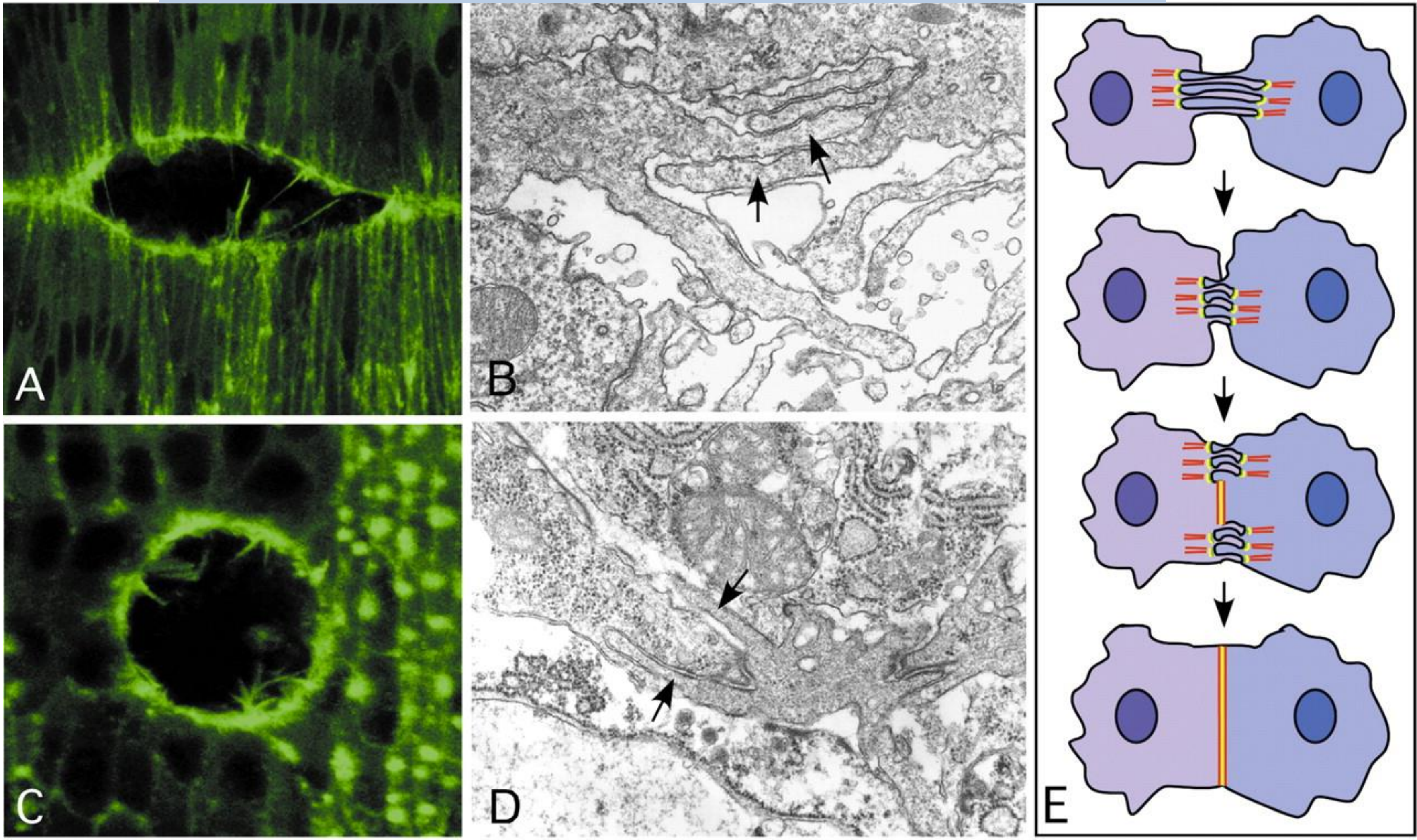


Science. 2008 Sep 19;321(5896):1683-6. doi: 10.1126/science.1157052.

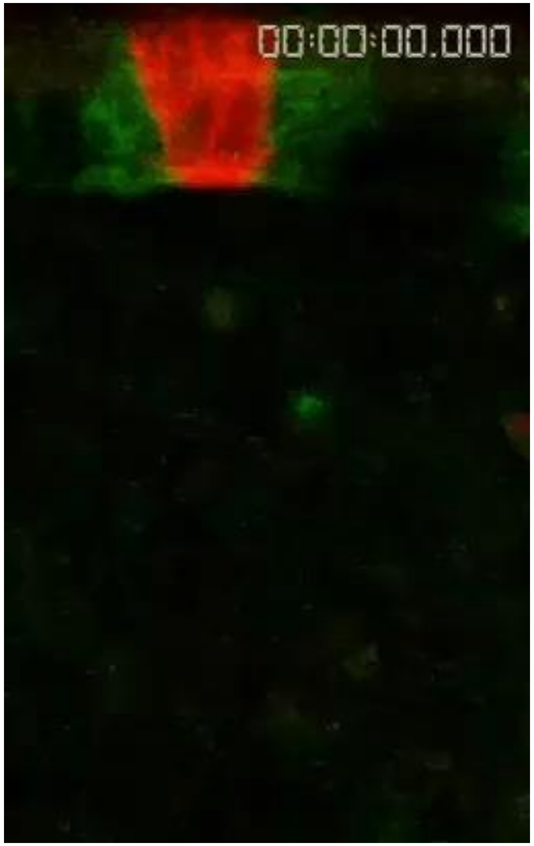
Apoptotic force and tissue dynamics during Drosophila embryogenesis.

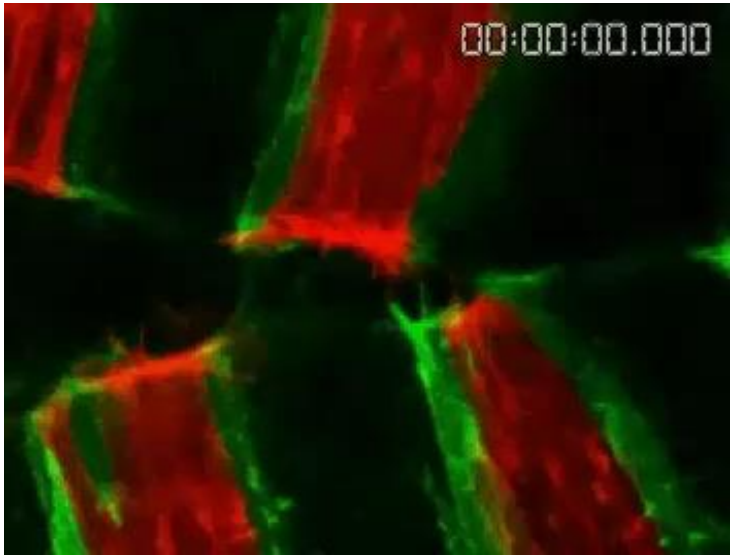
Toyama Y[1], Peralta XG, Wells AR, Kiehart DP, Edwards GS.

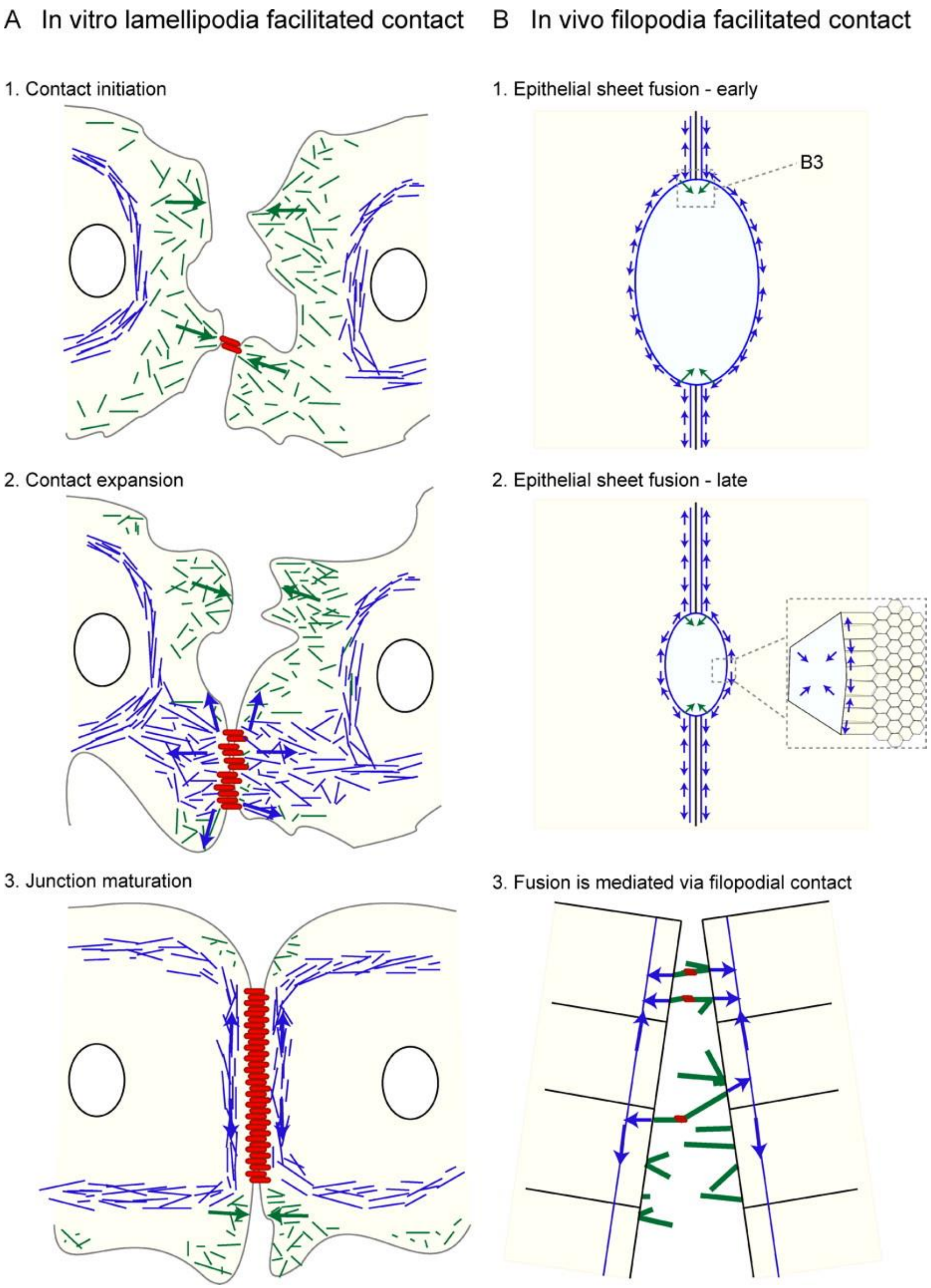
Drosophila dorsal closure (~ "Wound healing")



Drosophila dorsal closure







A In vitro lamellipodia facilitated contact

1. Contact initiation

2. Contact expansion

3. Junction maturation

B In vivo filopodia facilitated contact

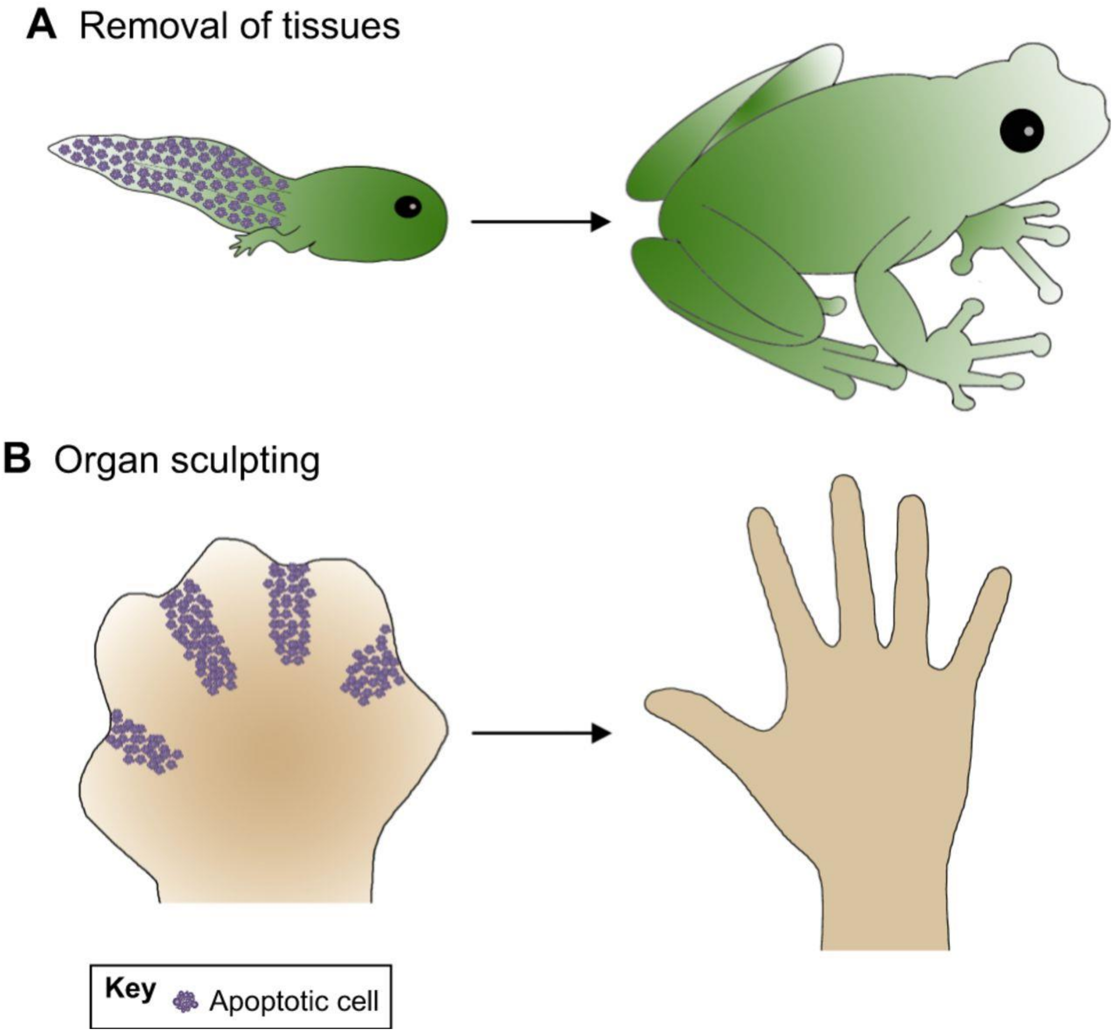
1. Epithelial sheet fusion - early

2. Epithelial sheet fusion - late

3. Fusion is mediated via filopodial contact

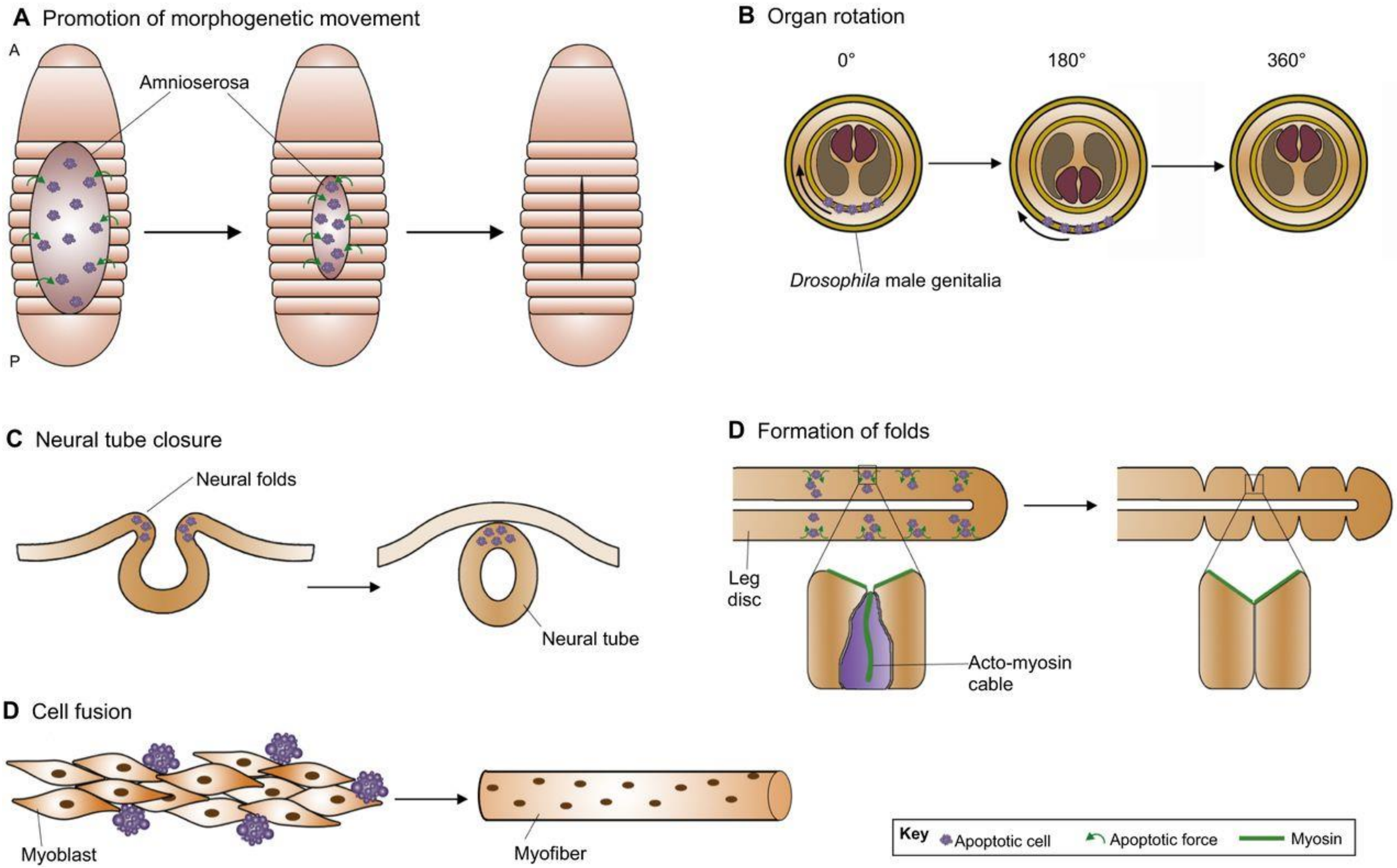
Apoptosis

Roles for apoptosis in tissue and organ sculpting



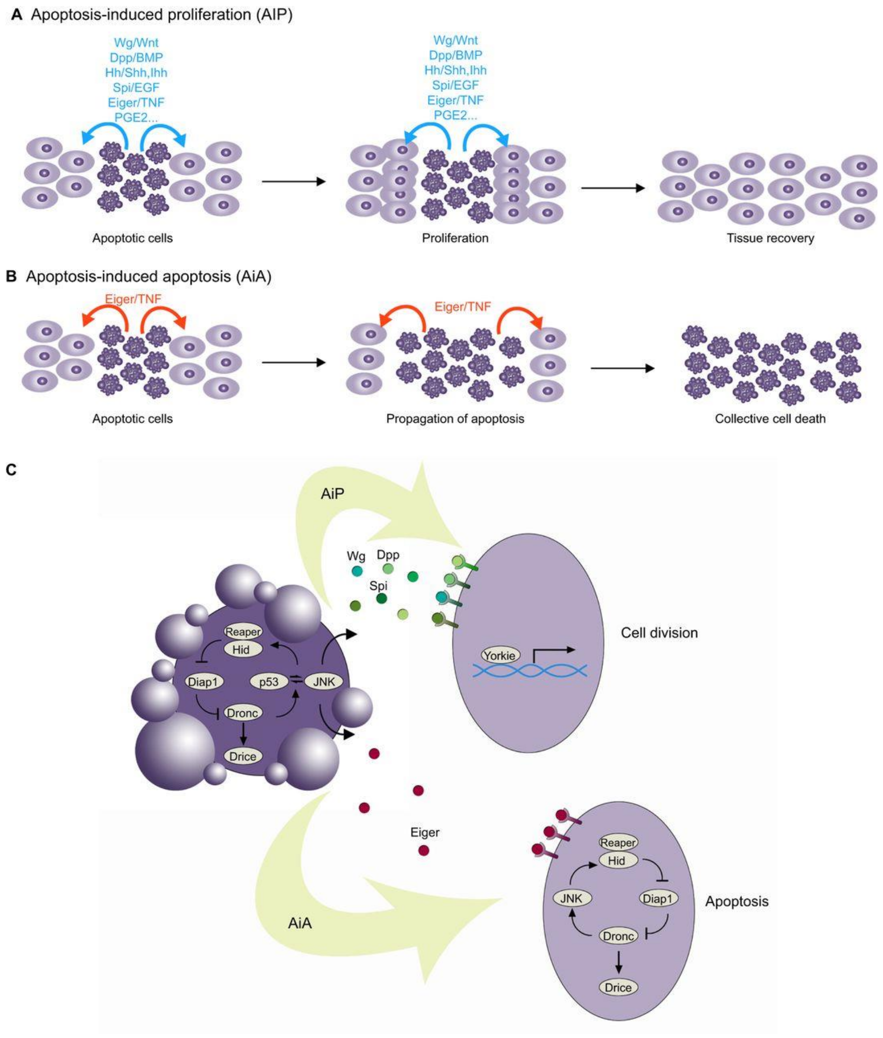
Ainhoa Pérez-Garijo, and Hermann Steller Development 2015;142:3253-3262

Apoptosis as a mechanism to promote movement and shape tissues.



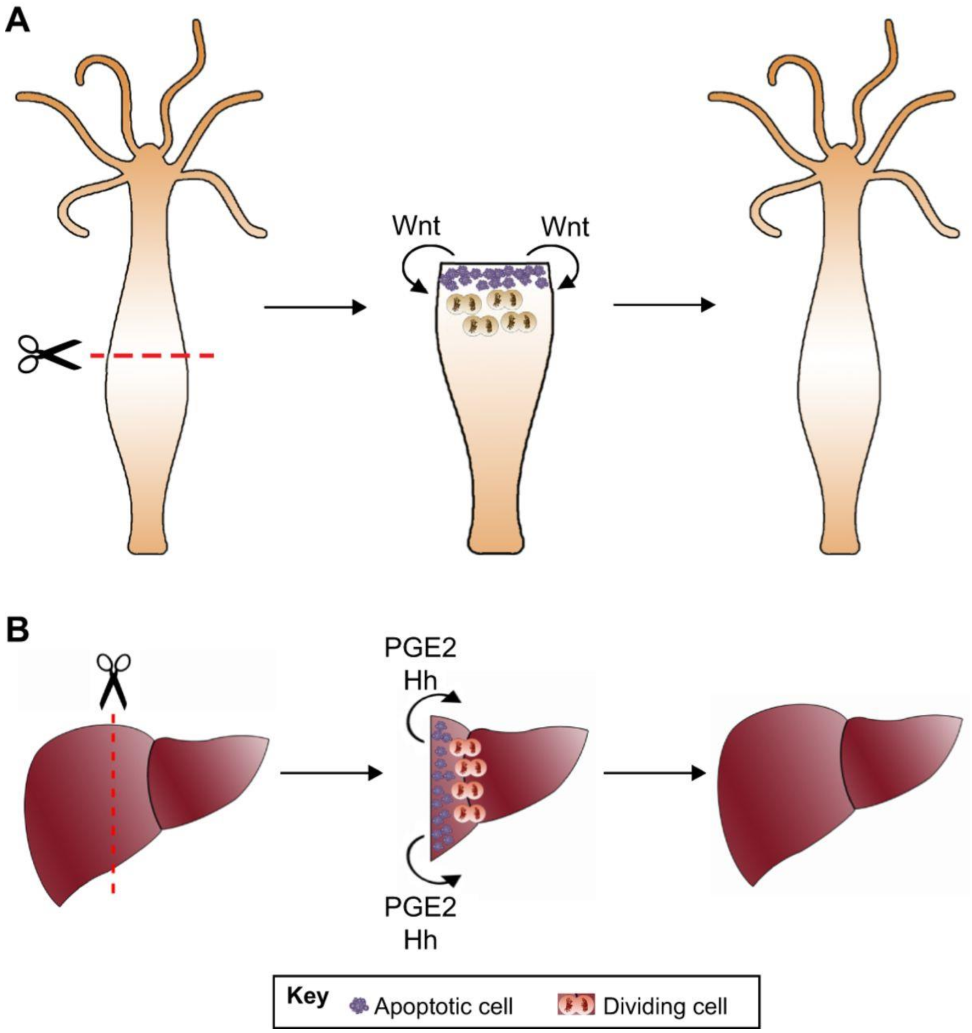
Ainhoa Pérez-Garijo, and Hermann Steller Development 2015;142:3253-3262

Signaling by apoptotic cells.



Ainhoa Pérez-Garijo, and Hermann Steller Development 2015;142:3253-3262

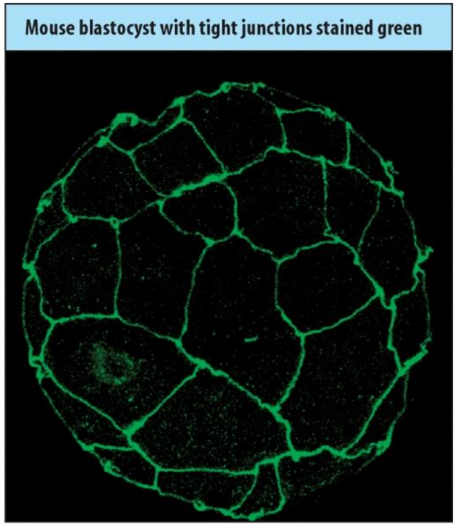
The role of apoptosis in regeneration.

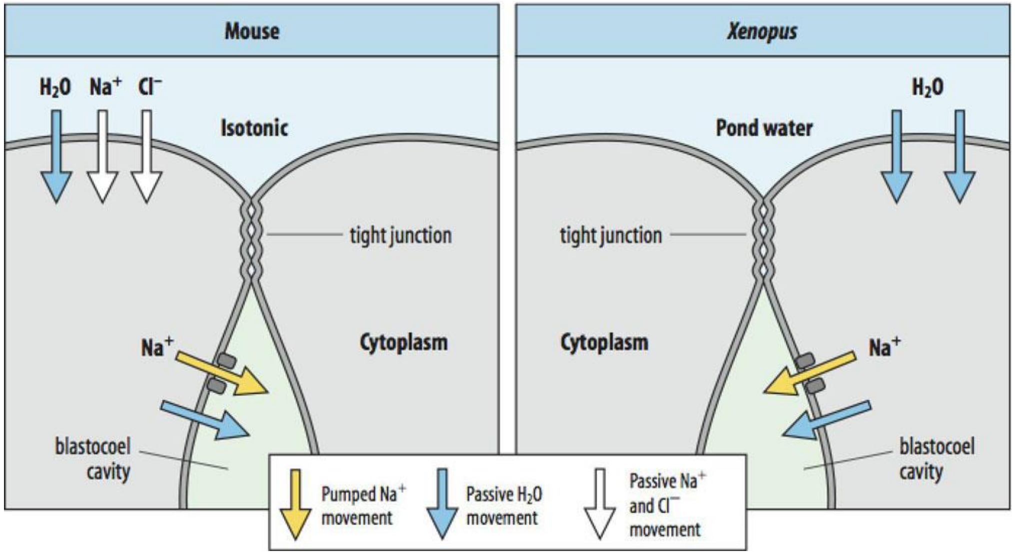


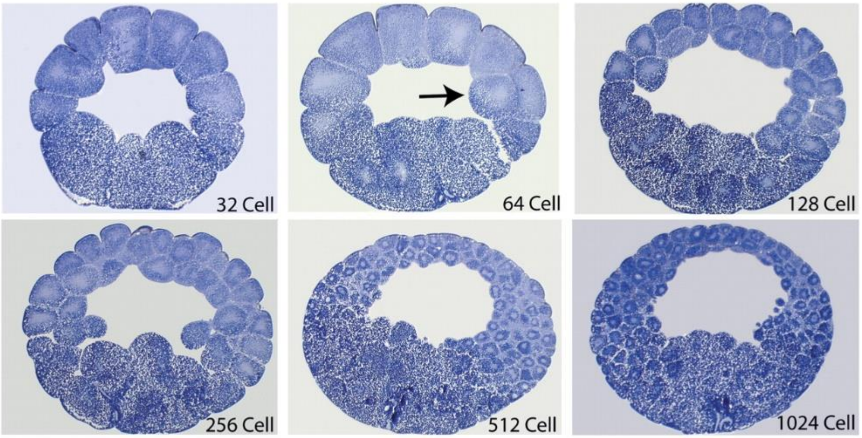
Ainhoa Pérez-Garijo, and Hermann Steller Development 2015;142:3253-3262

Cavitation

Cavitation: Blastocoel


Mouse blastocyst with tight junctions stained green





Tubulogenesis

Development
dev.biologists.org

THE COMPANY OF Biologists

Tubulogenesis

M. Luisa Iruela-Arispe and Greg J. Beitel

The importance of tubes

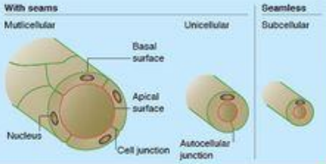
Epithelial and endothelial tubes are essential for moving nutrients and waste around the body in almost all metazoans. Despite the similarity in final architecture, tubes form via a remarkable variety of mechanisms.

The importance of tube formation is underscored by the devastation of diseases resulting from abnormal tubulogenesis, including polycystic kidney disease (afflicting ~1 in 800 people) and spina bifida (afflicting ~1 in 1000 births). Effective therapy requires a better understanding of the mechanisms by which tubes are formed.

Tube organization

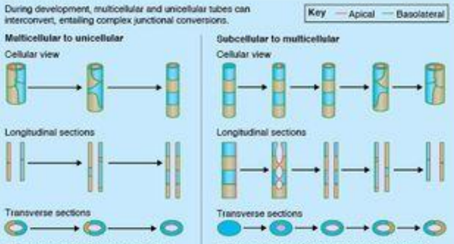
Tube types

Multicellular tubes enclose lumens, with several cells around the circumference connected by intercellular junctions or 'seams'. Unicellular tubes enclose lumens with a single cell around the circumference joined with an autocellular junction. A subcellular (seamless) tube has no cell-cell junction as the lumen forms in the cytoplasm.



Converting between tube types

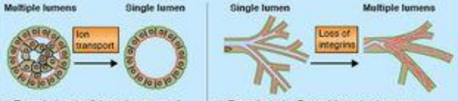
During development, multicellular and unicellular tubes can interconvert, entailing complex junctional conversions.



- Example: during *Drosophila* tracheal dorsal branch morphogenesis, a seamed multicellular tube converts to a seamed unicellular tube[1].
- Example: during *Ciona* notochord development, a seamless subcellular tube forms and then converts to a seamed multicellular tube[2].

Lumen coherency

Multiple mechanisms exist to ensure a single continous lumen in a tube.



- Example: in zebrafish, coalesecence of nascent intestinal lumens requires ion transport[3].
- Example: in the *Drosophila* tracheal system, maintaining single lumens within a unicellular tube requires integrins[4].

Cellular mechanisms of lumen formation

Budding

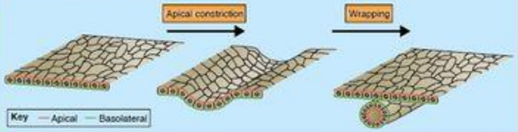
Cells invaginate from a sheet or an existing tube to form a new tube or branch.

- Examples: mammalian lung, kidney, angiogenesis, *Drosophila* salivary gland, trachea, hindgut and dorsal appendages.

Wrapping

A line of cells encloses a lumen by invaginating from a sheet of cells and then pinching off.

- Example: the neural tube in most vertebrates (below).



Lumen entrapment

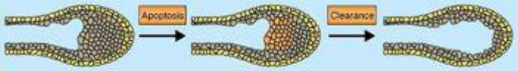
Cells enclose a lumen as they encounter each other. Wrapping is a form of lumen entrapment.

- Example: *Drosophila* embryonic heart[5,6].

Cavitation

Cells form a solid cord and then create lumenal space by apoptosis or autophagy.

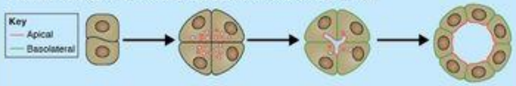
- Example: mammalian mammary gland.



Cord hollowing

Cells form a solid cord and then create a lumen by establishing apical/basal polarity and separating apical surfaces.

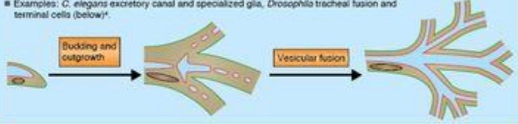
- Examples: vertebrate vasculature, zebrafish and *Ciona* notocord and MDCK tubules.



Cell hollowing

Single cells create a subcellular lumen, in which apical surfaces typically face the lumen.

- Examples: *C. elegans* excretory canal and specialized glia, *Drosophila* tracheal fusion and terminal cells (below)[4].

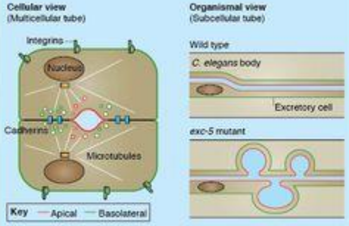


Molecular mechanisms of lumen formation and size control

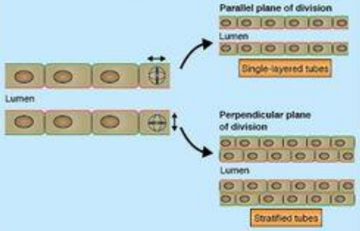
Organ function is critically dependent on forming lumens of specific sizes. Creating lumens and controlling their size require multiple molecular pathways. Some of these are shared, but others are unique to either tube formation or size control.

Mechanisms used for both lumen formation and tube size control

Vesicular trafficking
Delivery of membrane surface protein (below, cellular view) is essential for initial lumen formation and tube size control. In *C. elegans*, loss of the guanine nucleotide exchange factor EXC-5 causes defects in endocytic trafficking, resulting in cysts developing in the excretory canal[7] (organismal view).

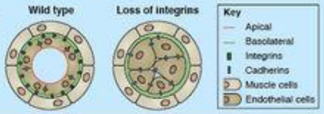


Cell polarity
Lumen formation requires acquisition of cell polarity with distinct apical (lumenal) and basal (ablumenal) surfaces (left figure in vesicular trafficking). Through poorly understood mechanisms, cell polarity also orients (polarizes) cell division to create tubes with multicellular or single-layered walls, and can control tube length and diameter.



ECM and adhesion
ECM interacting with integrins and other cell adhesion receptors can direct epithelial/endothelial cell polarity and establish apical and basal cell surfaces (above, cellular view). During angiogenesis, loss of integrins prevents relocalization of cell adhesion complexes and arrests lumen formation[8] (left).

In addition, ECM contacting the apical cell surface can control tube size.

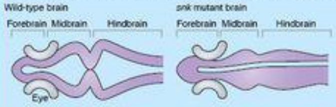


Cytoskeleton
The cyoskeleton has many essential functions in lumen formation and tube size control, including enabling polarized secretion (above left, cellular view), making cilia and conferring mechanical properties of cell membranes.

Mechanisms that separate lumenal surfaces to form open tubes

Creating lumenal surfaces does not automatically create a functional tube. Separating surfaces can require specific processes.

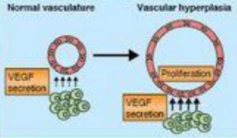
Hydrostatic pressure
Ion and fluid transport generates hydrostatic pressure and can drive lumen expansion. During zebrafish brain ventricle development, Na^+/K^+-ATPase mutations (*snk*) block fluid transport and lumen opening but not lumen formation[9].



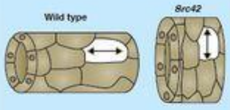
Electrostatic repulsion
Electrostatic repulsion can drive lumen expansion. In the developing mouse aorta, negatively charged sialic acid glycosylation is required for opening lumens (left). Loss of sialic acid blocks lumen opening[10] (right).

Mechanisms that control lumen size after tube formation

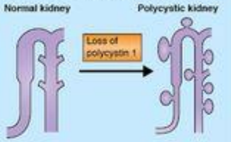
Cell number
In some – but not all – tubes, changes in cell number drive changes in tube size. For example, in vertebrate vascular development, an excess of soluble VEGF can drive endothelial cell proliferation and produce abnormally large vessels[11].



Cell shape/orientation
Mutations in PCP pathways increase cell and tube length. In *Src42* mutants, but not PCP mutants, cells are misoriented and tubes are shorter and wider in diameter than in wild type[12,13].



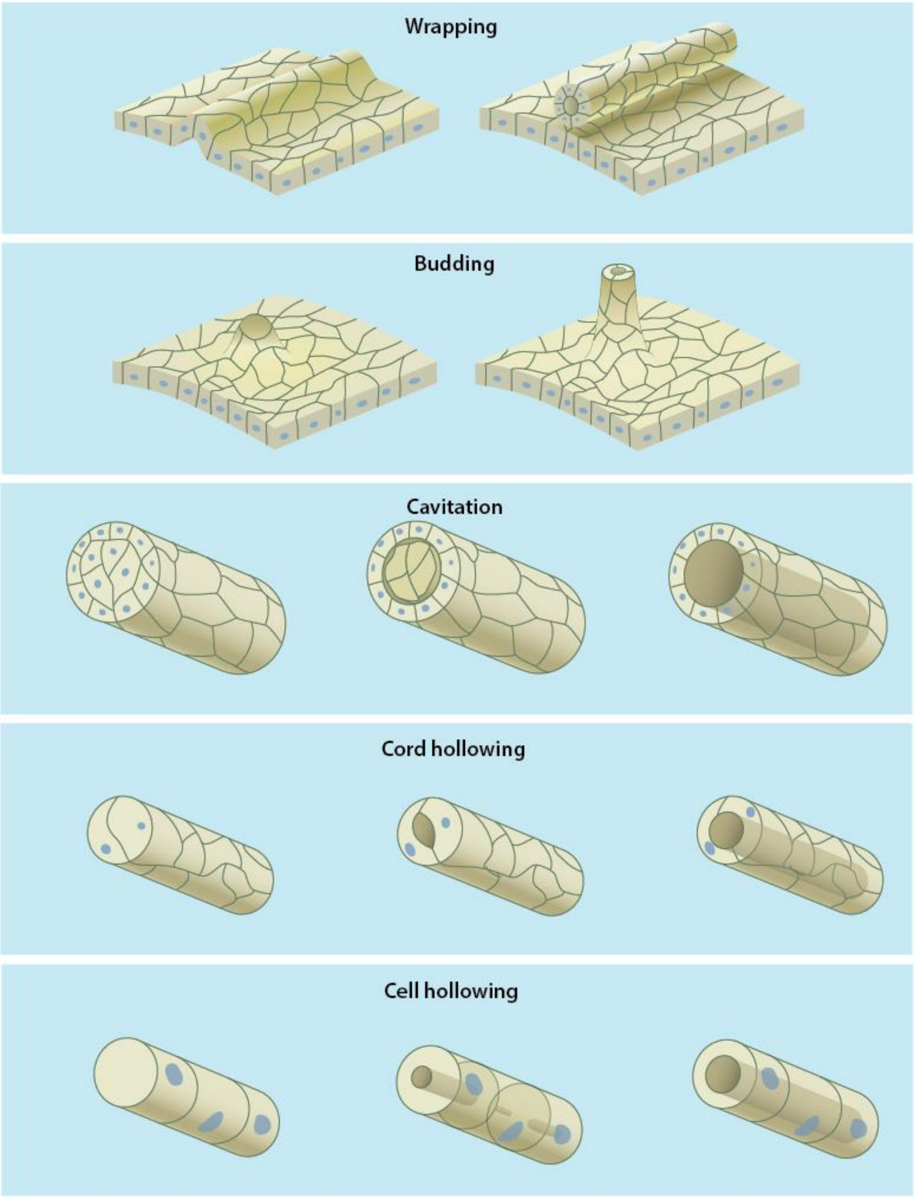
Fluid pressure and flow
Lumenal pressure and flow can dramatically affect tube morphogenesis and function. Failure to detect flow appears to underlie polycystic kidney disease.



References: [1]Ribeiro et al., 2004; [2]Dong et al., 2009; [3]Bagnat et al., 2007; [4]Levi et al., 2006; [5]Medioni et al., 2008; [6]Santiago-Martinez et al., 2008; [7]Mattingly and Buechner, 2011; [8]Zovein et al., 2010; [9]Lowery et al., 2009; [10]Strilić et al., 2010; [11]Lee et al., 2005; [12]Förster and Luschnig, 2012; [13]Nelson et al., 2012. For details, see main article.

Abbreviations: ECM, extracellular matrix; MDCK, Madin-Darby canine kidney; PCP, planar cell polarity; *snk*, *snakehead* (*atp1a1*); VEGF, vascular endothelial growth factor.

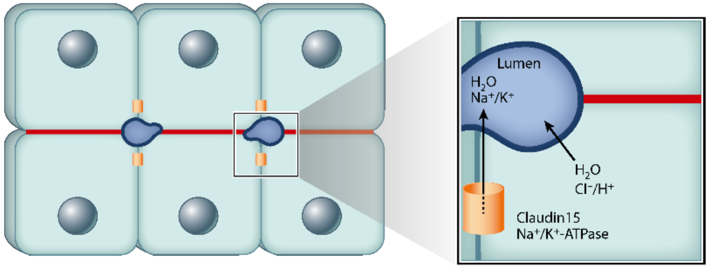
Various modes of tube formation



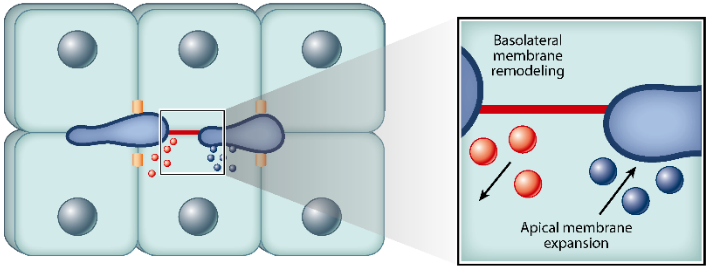
https://www.mechanobio.info/

Various modes of tube formation

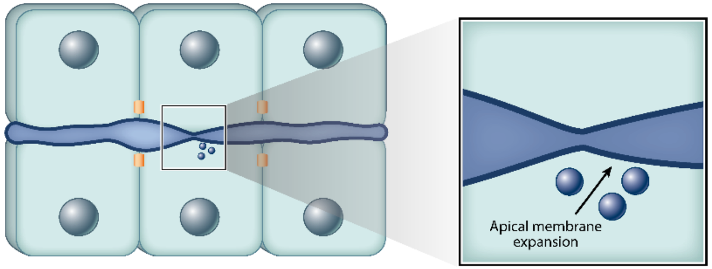
a Lumen expansion through paracellular ion transport



b Apical membrane remodeling through vesicle transport



c Apical lumen resolution and expansion

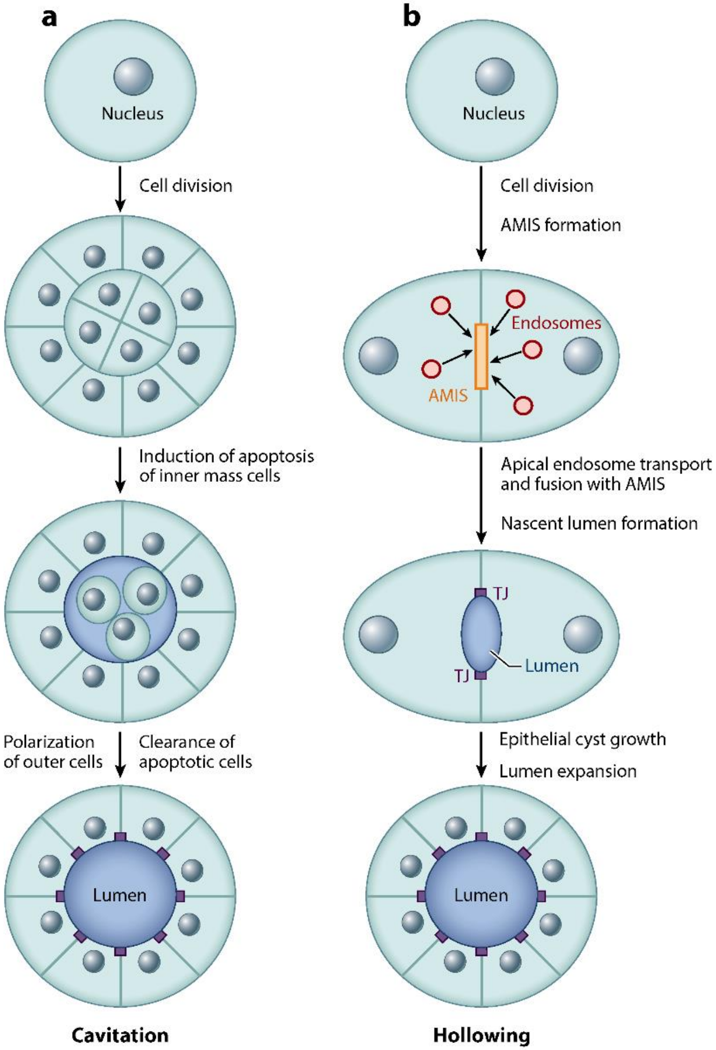


Blasky AJ, et al. 2015.
Annu. Rev. Cell Dev. Biol. 31:575–91

Annual Reviews

Various modes of tube formation

AMIS, apical membrane initiation site

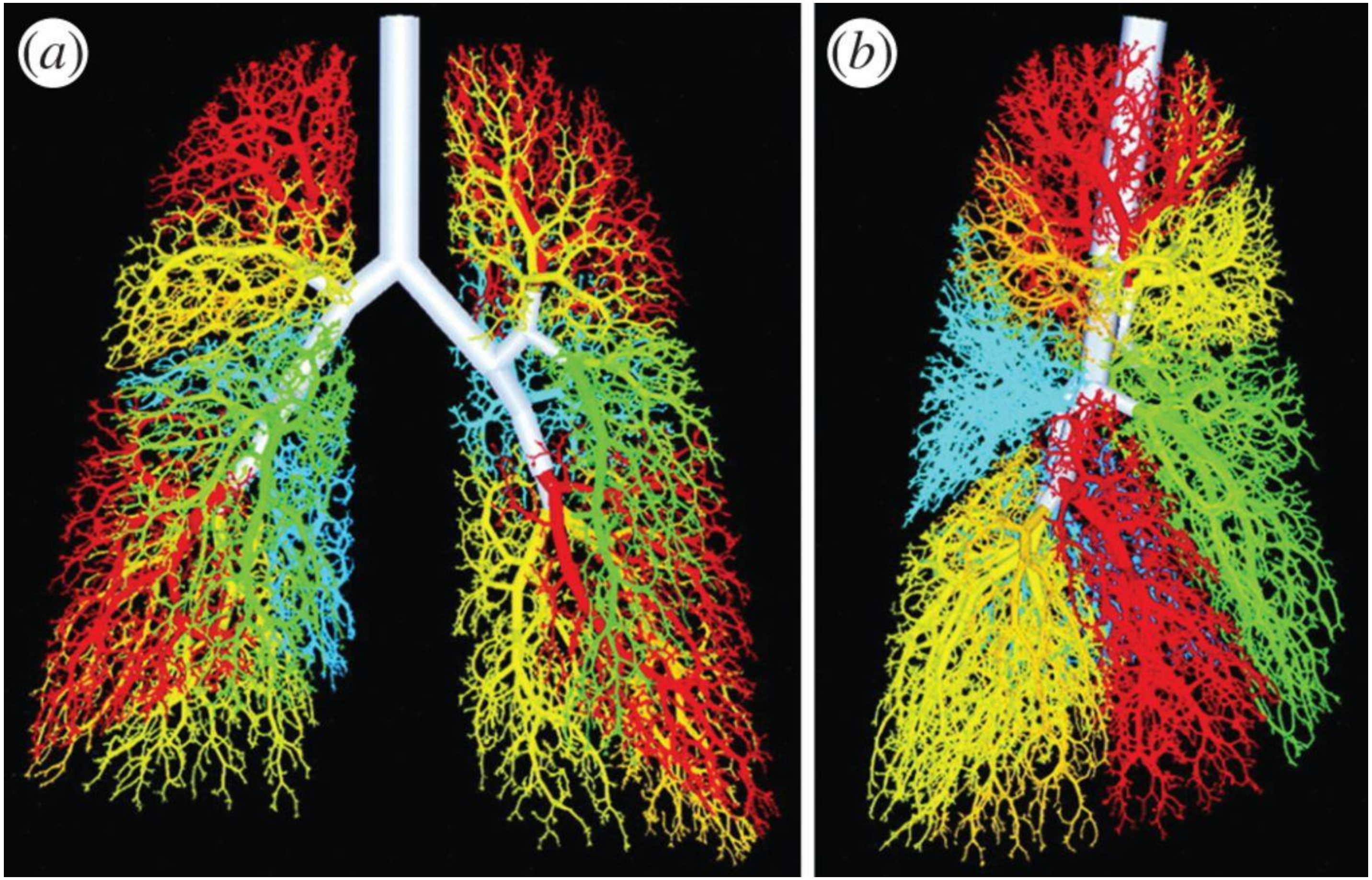


Blasky AJ, et al. 2015.
Annu. Rev. Cell Dev. Biol. 31:575–91

Annual Reviews

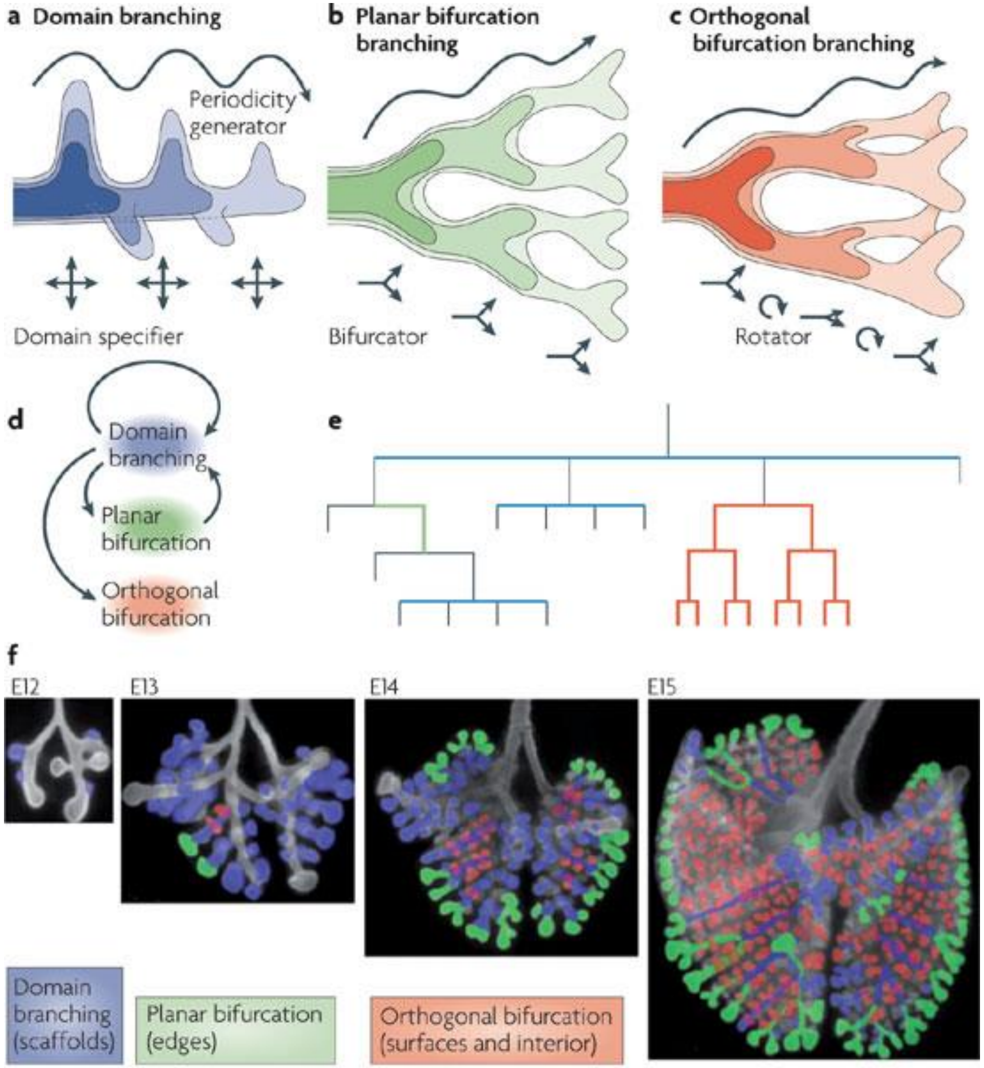
Branching

lung



Branching

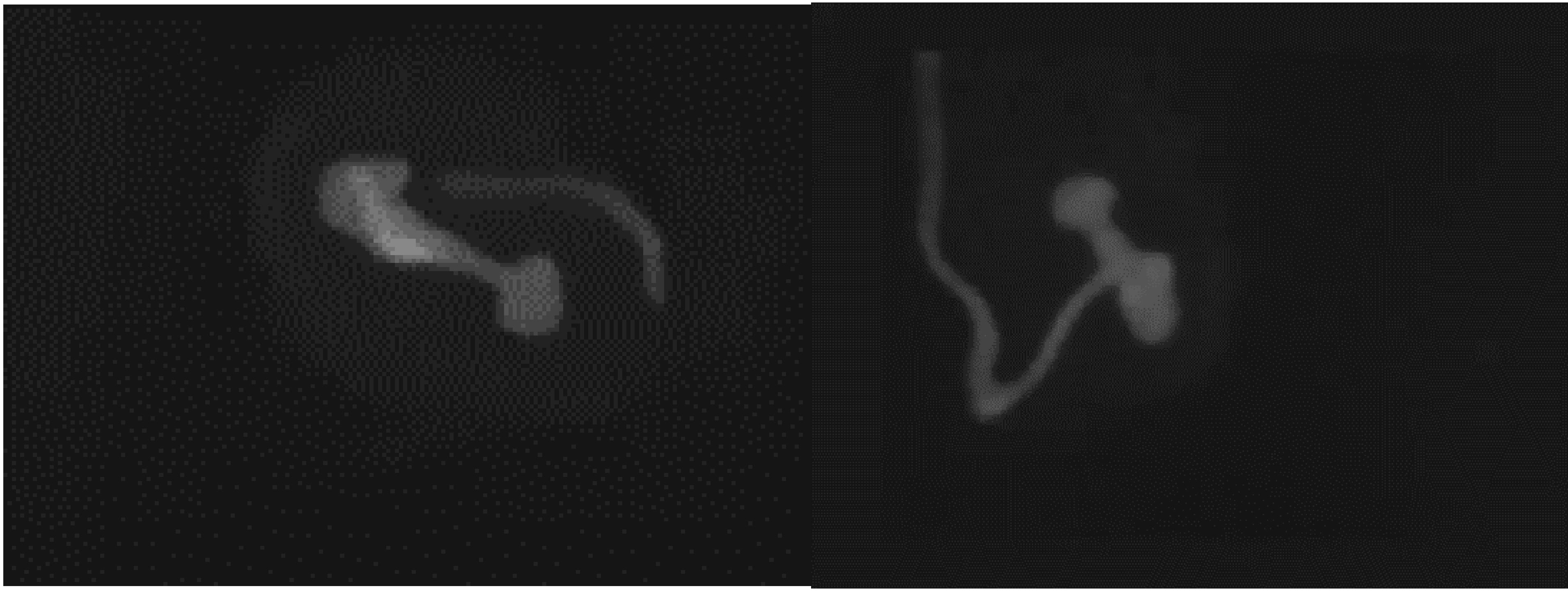
Lung



Nature Reviews | Molecular Cell Biology

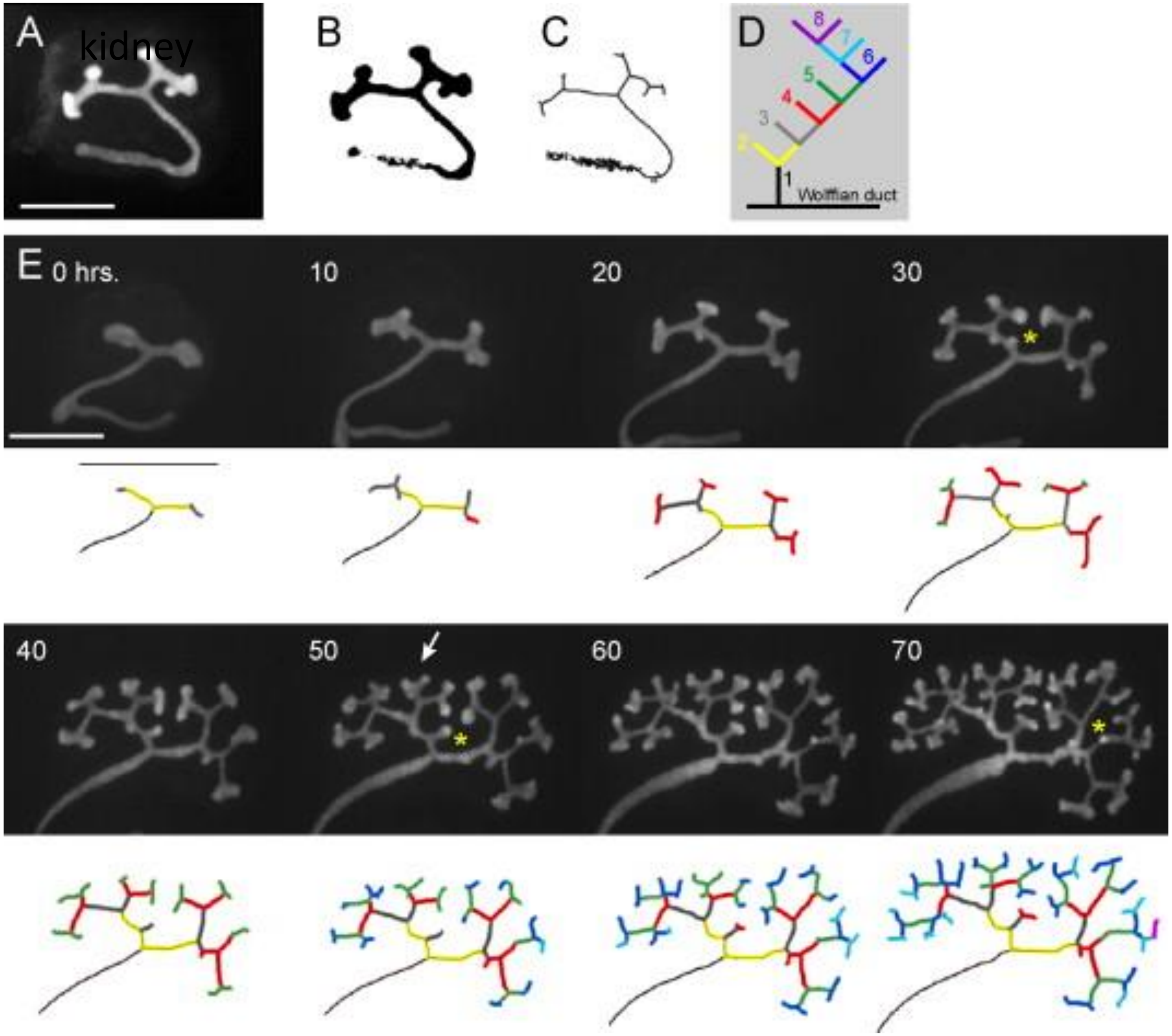
Branching

kidney



Tomoko Watanabe, Frank Costantini **Real-time analysis of ureteric bud branching morphogenesis in vitro**
Developmental Biology, Volume 271, Issue 1, 2004, 98–108

Branching



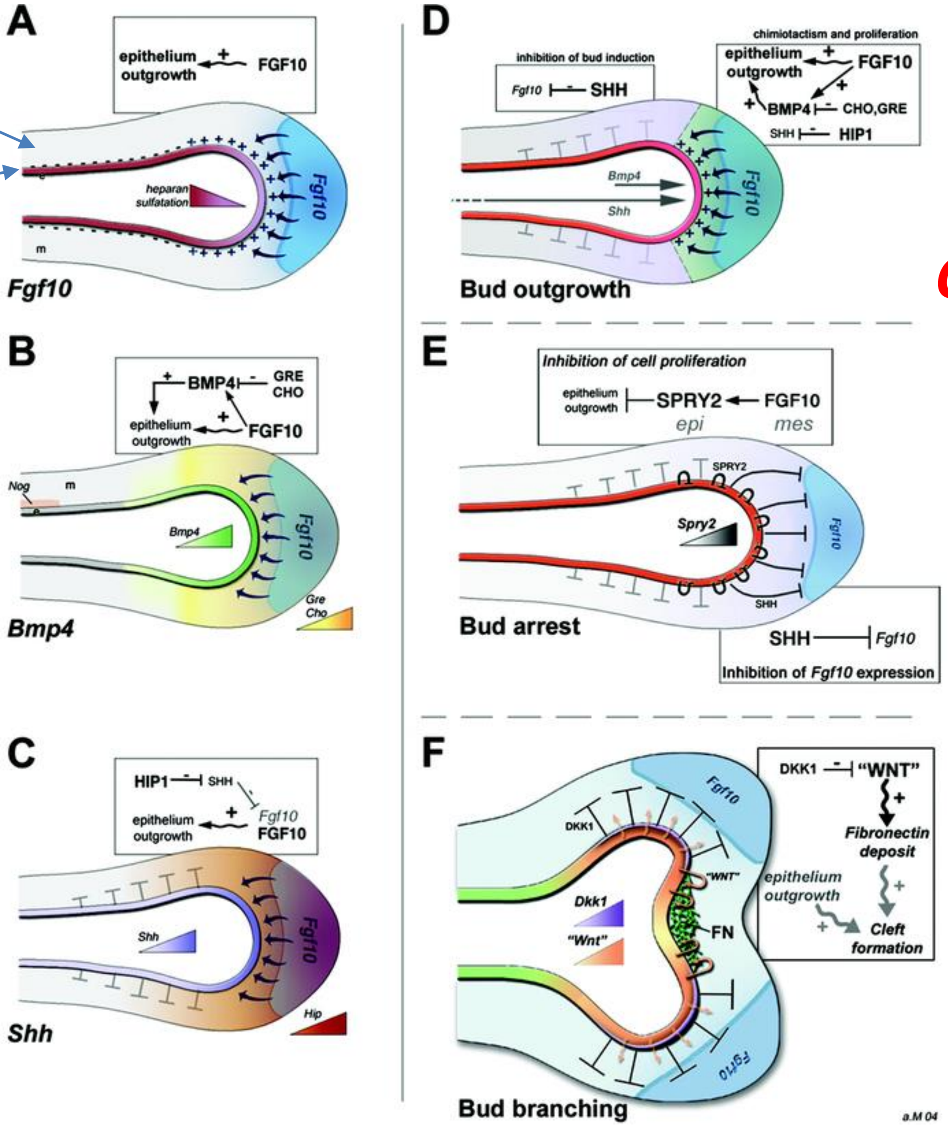
Tomoko Watanabe, Frank Costantini **Real-time analysis of ureteric bud branching morphogenesis in vitro**
Developmental Biology, Volume 271, Issue 1, 2004, 98–108

Branching

mesenchyme

epithelium

lung

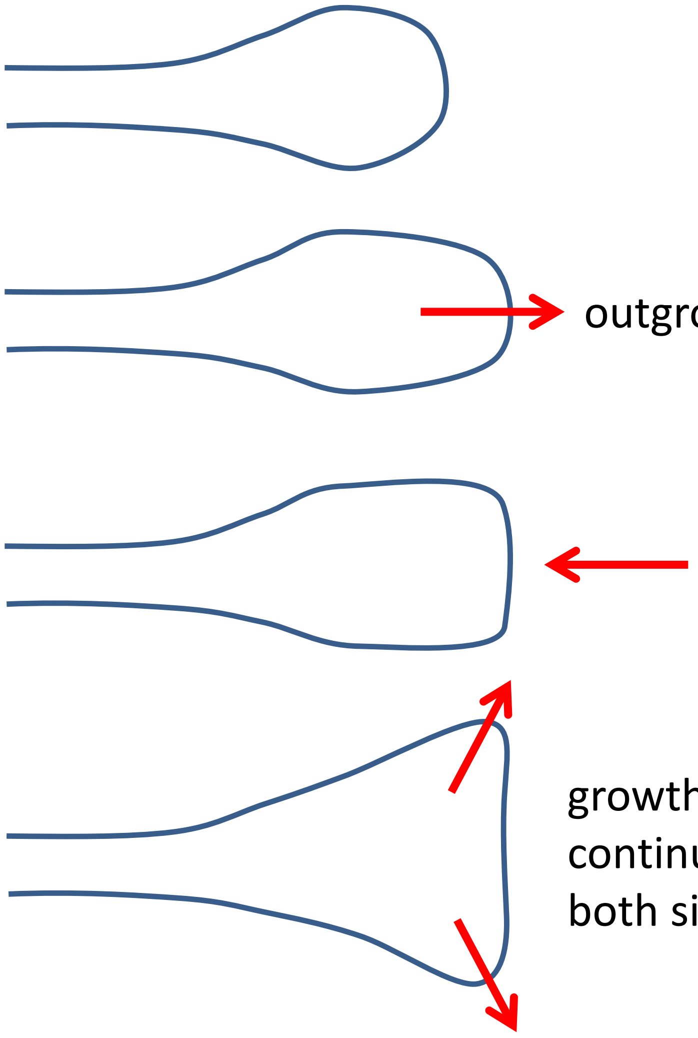


Complex signals

Branching (lung)

The figure models the functional integration of key growth factor signaling pathways in lung bud outgrowth, bud arrest, and bud branching. Panel A depicts the function of FGF10 to stimulate bud outgrowth. Fgf10 is expressed in the distal mesenchyme so that a decreasing gradient of FGF10 acts to stimulate chemotaxis of the bud tip toward the subpleural source of FGF10. Heparan sulfation is also important for FGF function. Panel B depicts the function of BMP4 to stimulate lung branch tip outgrowth together with FGF10. FGF10 is shown stimulating BMP4 expression, whereas the ligand binding proteins Gremlin (GRE) and Chordin (CHO) exert negative modulation on BMP4. Panel C depicts the functional interaction of SHH and Hip with FGF10. SHH inhibits Fgf10 expression away from the branch tip. However at the branch tip, Hip inhibits SHH, releasing the SHH mediated inhibition of Fgf10 expression. Panel D superimposes the functional integration of Fgf10, Bmp4, and Shh to mediate the delicate balance between chemotaxis and proliferation leading to bud induction versus inhibition of bud outgrowth. Panel E depicts the events that may determine interbranch length by leading to arrest of bud outgrowth. FGF10 induces SPRY2, which in turn inhibits epithelial outgrowth. Meanwhile, in more proximal regions suppression of branching is mediated by SHH, which inhibits Fgf10 expression outside the peripheral mesenchyme. Panel F depicts a potential mechanism for bud tip splitting in which WNT signaling drives Fibronectin (FN) deposition between the branch tips, leading to epithelial cleft formation. Meanwhile, Dickkopf (DKK1) inhibits Wnt signaling away from the cleft, leading to lower levels of FN deposition where clefting does not occur.

Branching



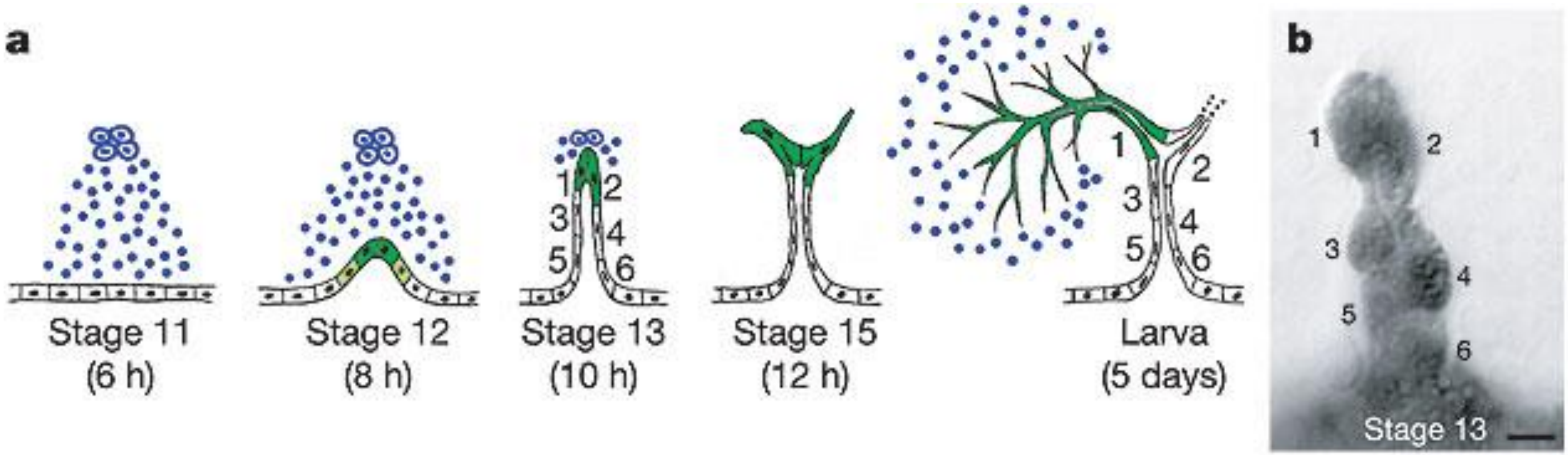
outgrowth

inhibition of
growth at tip

growth
continues on
both sides

Branching

Social interactions among epithelial cells during tracheal branching morphogenesis
Amin S. Ghabrial & Mark A. Krasnow
Nature **441**, 746-749(8 June 2006)

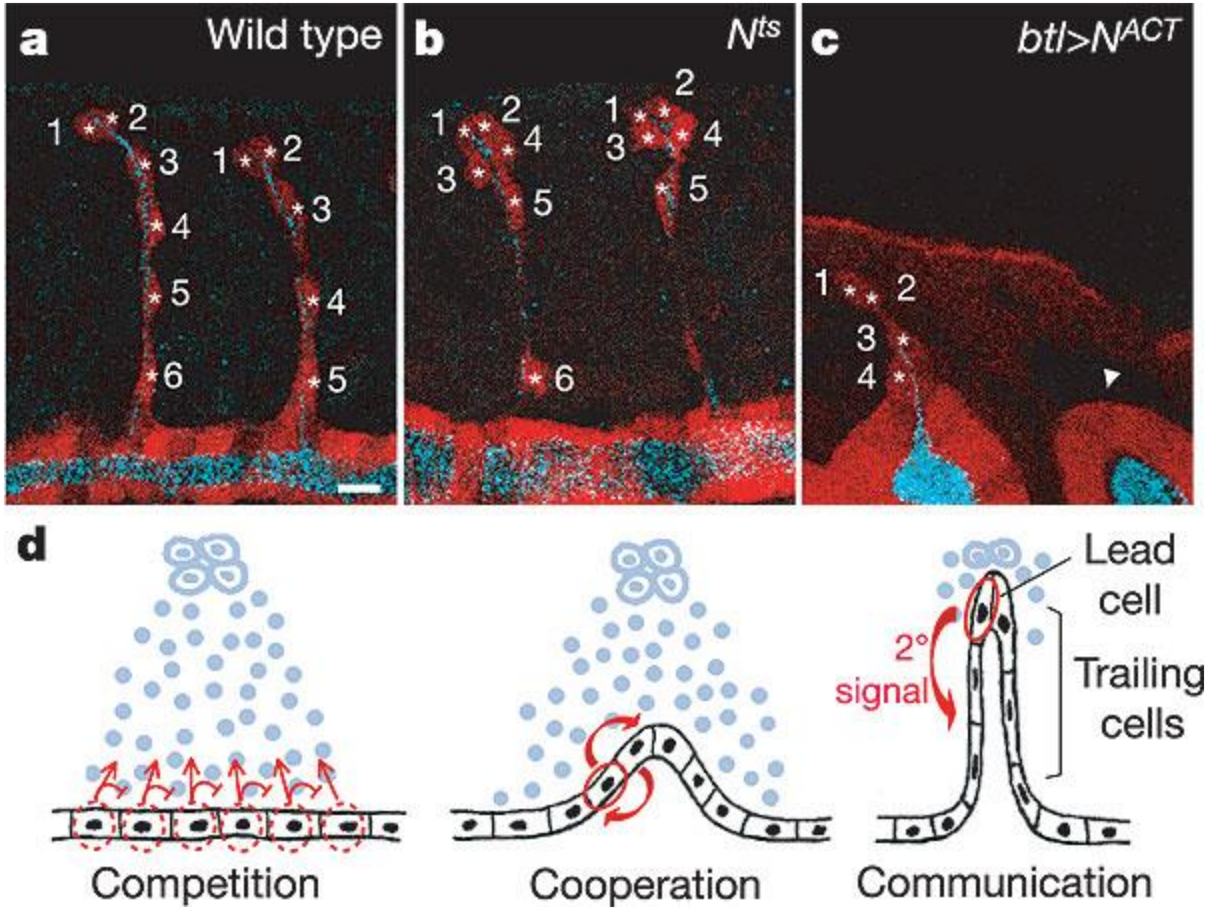


a, Diagram of dorsal branch (DB) *budding from tracheal epithelium (black; DB cells numbered 1–6) at the developmental stages and times indicated. Nearby cells (blue) secrete Branchless FGF (blue dots), which activates Breathless (Btl) FGFR on tracheal cells, inducing migration and tube formation. Bnl also induces secondary branching genes (for example pointed) in cells (green) that form unicellular secondary branches (stage 15). Subsequently, DB1 (terminal cell) forms terminal branches in response to Bnl expressed by hypoxic larval cells. DB2 (fusion cell) forms a branch that fuses (dotted lines) to a contralateral DB (not shown). DB3–6 cells form DB stalk. b, Micrograph of budding DB (stage 13). Nuclei are black; cytoplasm is grey. Cells here are arranged side by side, but subsequently the stalk cells intercalate. Reprinted with permission (ref. 8). Scale bar, 2.5 microm.*

Branching

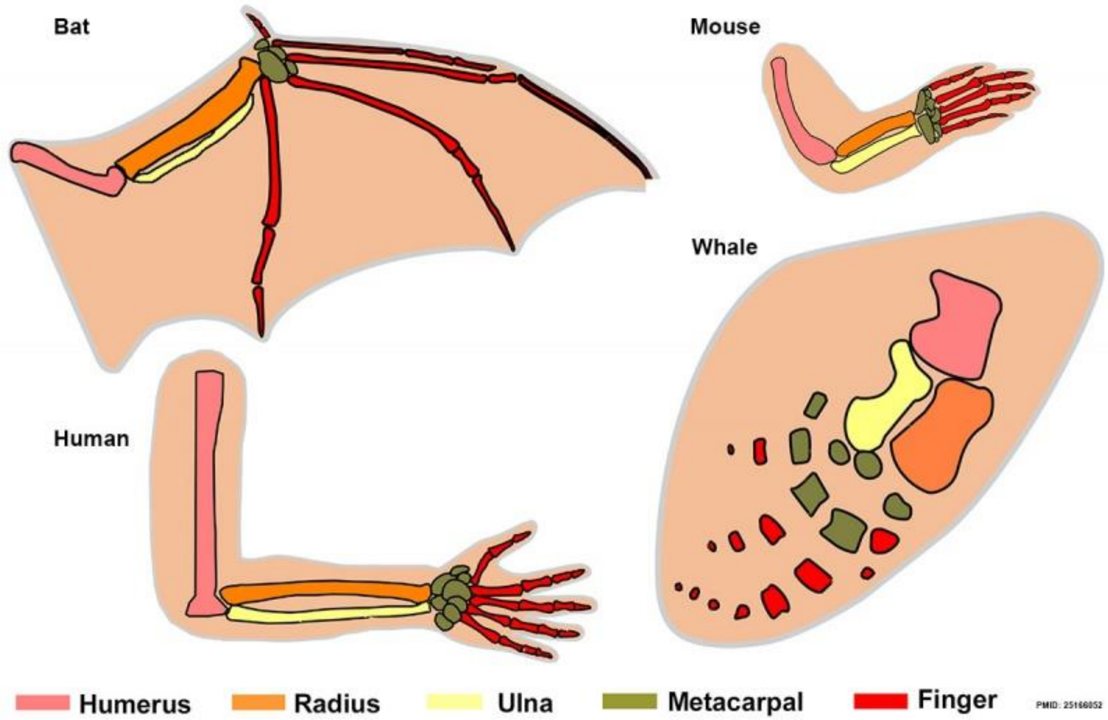
Role of Notch signalling in lateral inhibition

Social interactions among epithelial cells during tracheal branching morphogenesis
Amin S. Ghabrial & Mark A. Krasnow
Nature **441**, 746-749(8 June 2006)



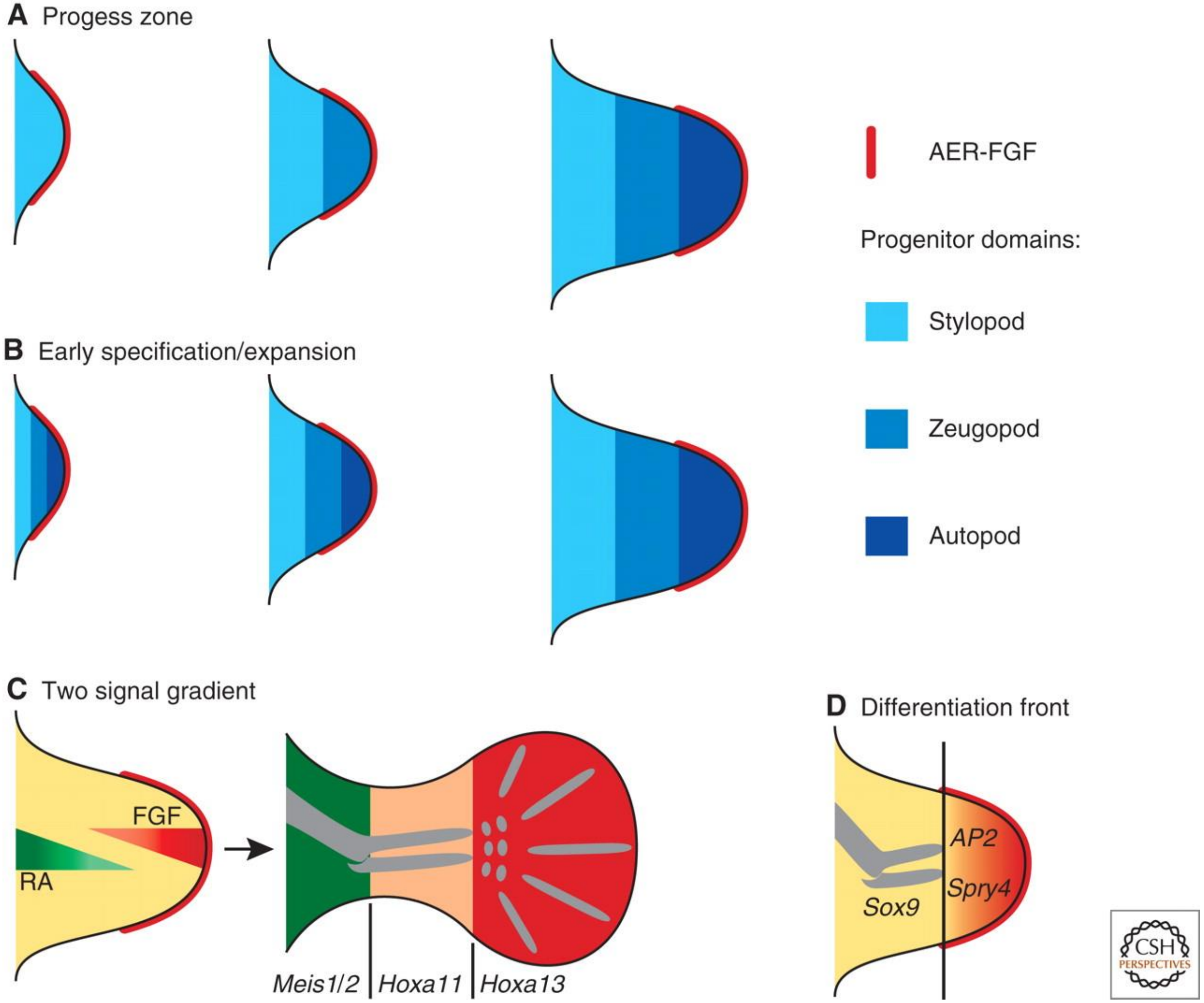
a–c, Fluorescent micrographs of two DBs (lateral view) in stage 15 wild-type embryo (a), Nts embryo shifted to non-permissive temperature for 6 h during branch budding (b) and btlGal4 > UAS-NACT embryo that expressed activated N throughout the tracheal system (c). All embryos carried btlGal4 and UAS-GFP transgenes and were double-stained for GFP (red; tracheal cell marker) and Vermiform (cyan; luminal marker). a, Cells in wild-type DBs are evenly distributed (nuclei are numbered and indicated by asterisks). b, N inactivation caused the migration of extra cells to the DB tip. c, Constitutive N activity inhibited outgrowth, particularly in posterior metameres in which some DBs completely failed to bud (arrowhead). Scale bar, 5 microm. d, Social interactions between tracheal cells during budding. The three panels show budding tracheal cells expressing the Btl FGFR moving towards a Bnl FGF signalling centre, as in Fig. 1a. The first panel illustrates cell competition: cells move towards the lead position and inhibit their neighbours from doing the same. The second panel illustrates cell cooperation: a cell with less Btl activity allows one with more to move ahead of it. The third panel illustrates cell communication: the lead cell sends a secondary (2 °) signal to the trailing cells, inducing them to follow the lead cell and activating a tubulogenesis programme. Cells also communicate via Notch-mediated signalling as they compete for the lead position (inhibition arrow in first panel).

Limb morphogenesis



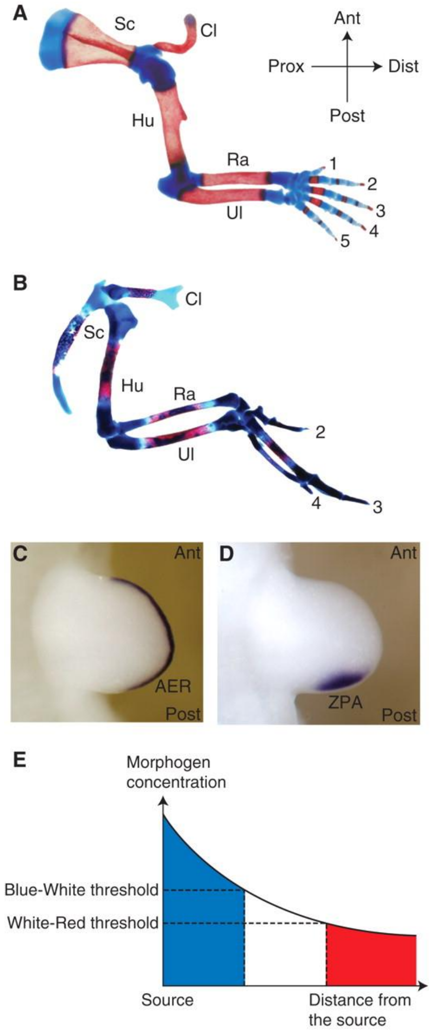
PMID: 25166052

Models and mechanisms of proximal distal limb axis morphogenesis.



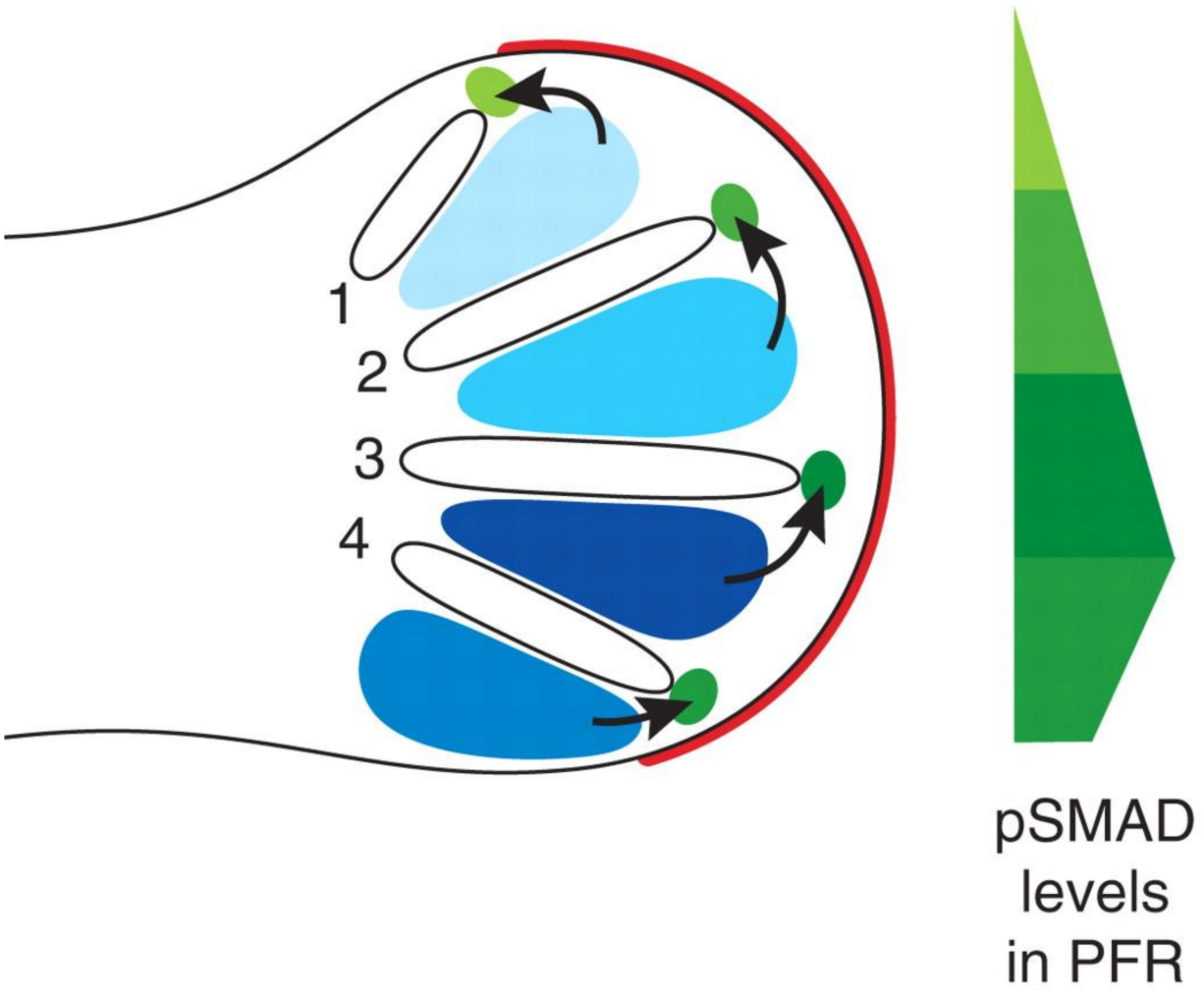
Jean-Denis Bénazet, and Rolf Zeller Cold Spring Harb Perspect Biol 2009;1:a001339

Two morpho-regulatory signaling centers control vertebrate limb-bud development.



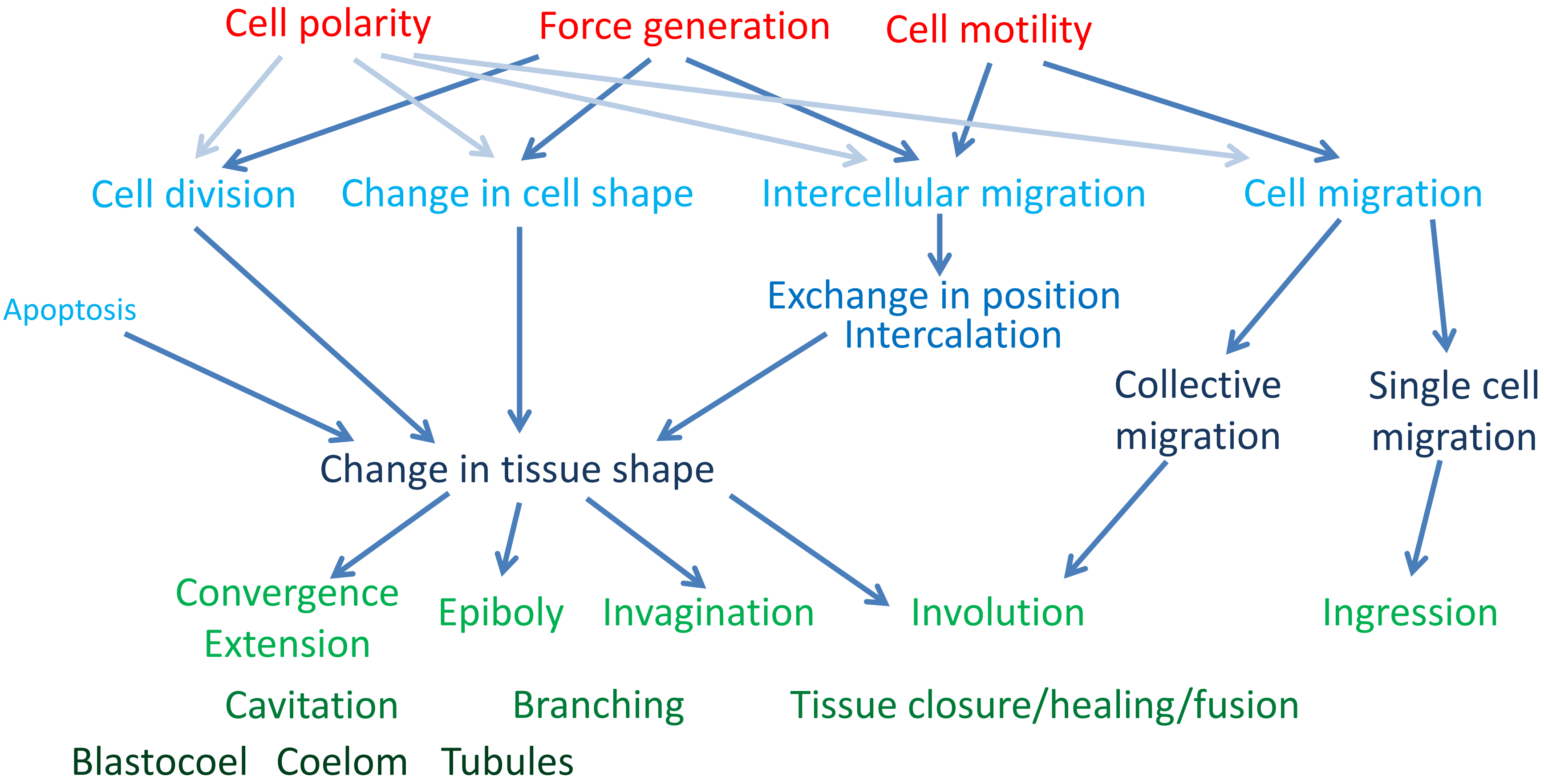
Jean-Denis Bénazet, and Rolf Zeller Cold Spring Harb Perspect Biol 2009;1:a001339

The role of BMP signaling from the interdigital mesenchyme in determination of digit identities.



Jean-Denis Bénazet, and Rolf Zeller Cold Spring Harb Perspect Biol 2009;1:a001339

Morphogenesis



Cell polarity
Force generation
Cell motility

Cell division
Change in cell shape
Intercellular migration
Cell migration

Apoptosis
Exchange in position
Intercalation
Collective migration
Single cell migration

Change in tissue shape

Convergence Extension
Epiboly
Invagination
Involution
Ingression

Cavitation
Branching
Tissue closure/healing/fusion

Blastocoel
Coelom
Tubules

Gastrulation
Neurulation
Segmentation
Organogenesis

Morphogenesis

Cellular “motors”	Force generation/ Cell motility (actin polymerization + actomyosin contractility)
Cellular processes	Cell division Change in cell shape Intercellular migration Cell migration
Tissular processes	Change in tissue shape Exchange in position Intercalation Collective migration
Morphogenetic events	Epiboly Invagination Involution Ingression Branching Tissue closure/healing Cavitation (Blastocoel, coelom, tubules)
Developmental events	Gastrulation Neurulation Segmentation Organogenesis